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Early life risk factors for cerebrovascular disease and depressive symptoms in later life

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Abstract

Cerebrovascular disease (CVD) can result in cerebral small vessel disease (cSVD) and structural brain changes such as decreased cortical volume, brain atrophy and cerebral infarcts which are major causes of stroke and dementia. CVD is also associated with increased depression and depressive symptoms in later life. Midlife vascular disease and adult socioeconomic status (SES) are well established risk factors but less is known about the effect of factors from earlier in life on CVD and depressive symptoms in later life.

A series of systematic reviews of current literature examining early life factors and stroke, cSVD and depression following stroke are presented at the beginning of this thesis. These reviews found that childhood IQ, education and childhood SES were associated with stroke and cSVD in later life. The reviews also found that education level was associated with depression following stroke. However few of the studies adjusted for vascular risk factors and adult SES.

Therefore this thesis aimed to investigate associations between birth and childhood factors and cerebrovascular disease and depressive symptoms, after adjustment for vascular risk factors and adult SES, in four community dwelling cohorts: the Stratifying Resilience & Depression Longitudinally (STRADL) cohort (n=280, 45% male, mean age= 62.1 (SD=4.1) years), the Dutch Famine Birth cohort (n= 151, 44% male, mean age 67.6 (SD=0.9) years), the Lothian Birth Cohort 1936 (LBC 1936, n= 865, 50% male, mean age 72.7 (SD=0.7) years), and the Simpson cohort (n=130, 31% male, mean age 78.5, (SD=1.5) years).

This Thesis first examined associations between (i) cSVD burden (ii) total and regional brain volumes and (iii) self-reported symptoms of depression and anxiety measured using the Hospital Anxiety and Depression Scale. All analyses were adjusted for age, sex, hypertension, smoking behaviour, adult SES and cognition. Neither cSVD nor brain volumes were associated with symptoms of anxiety. Higher white matter hyperintensity volumes, having one or more cerebral infarct and increased cerebral atrophy were associated with increased depressive symptoms independent of vascular risk factors and adult SES.

Secondly, this thesis examined associations between birth and childhood factors and cSVD burden and total and regional brain volumes. Each cohort was analysed

individually and then all available data meta-analysed. All analyses were adjusted for age, sex, hypertension, smoking behaviour, adult SES and other early life factors. Meta-analysis found that increasing birth weight was associated with decreased risk of lacunes across all cohorts. Placental weight, which was only available for the Simpson cohort, was associated with decreased risk total cSVD, WMH severity and volume and cerebral infarcts. In the LBC 1936 and Simpson cohort increasing childhood and premorbid IQ and more years of education were associated with fewer cortical infarcts. The association between premorbid and childhood IQ and infarcts was independent of education level. Across three cohorts low education level was associated with more microbleeds. These findings suggest that factors other than traditional vascular risk factors may contribute to cSVD and structural brain changes in later life.

Thirdly, this thesis examined associations between birth and childhood factors and self-reported symptoms of depression and anxiety measured using the Hospital Anxiety and Depression Scale (HADS) and the Quick Inventory of Depressive Symptoms (QIDS-16). All analyses were adjusted for age, sex, hypertension, smoking behaviour, adult SES and cognition In the Dutch Famine Birth Cohort people born before the famine had lower scores of depression and anxiety on the HADS compared to those exposed to famine in early gestation and those conceived after the famine. In the LBC 1936 increasing ponderal index was associated with lower depressive symptoms, increasing childhood and premorbid IQ were associated with lower symptoms of anxiety and depression. Lower educational attainment and some indicators of childhood SES were associated with higher symptoms of depression and anxiety.

Overall results suggest that early life factors, particularly childhood IQ, may contribute to structural brain changes and symptoms of depression and anxiety in later life, independent of vascular risk factors and other early life factors. Efforts to understand factors which may contribute to late life health, from the earliest stages of life, are important and may be used to inform changes in social policy. The effect sizes and potential impact of these findings suggest that larger sample sizes with more vascular disease and more depression are needed to robustly test these associations.

Lay summary

Cerebral small vessel disease (cSVD) is caused by damage to the blood vessels supplying the brain and can lead to stroke and dementia and psychological problems such as depression. The cause of cSVD is unclear but lifestyle factors such as high blood pressure, smoking and a bad diet increase risk of cSVD and stroke. Some research suggests that events in early life may also be important. These include birth factors such as birth weight and size at birth and factors in childhood such as childhood IQ, education and childhood socioeconomic status (SES).

This thesis begins with a review of the current scientific literature on early life factors and risk of cSVD, stroke and depression after stroke. It found that low childhood IQ, low education and low childhood SES were associated with an increased the risk of cSVD, stroke and depression after stroke. However, most of these studies did not consider the effect of other risk factors such as smoking when looking at these associations.

And so the aim of this thesis was to examine whether certain birth and childhood factors increased the risk of cSVD and symptoms of depression and anxiety in older adults. When looking at these associations the effect of age, sex, high blood pressure, smoking behaviour and adult SES were controlled for. Data were taken from four groups of healthy participants over the age of 60; the Stratifying Resilience & Depression Longitudinally (STRADL) cohort, the Dutch Famine Birth cohort, the Lothian Birth Cohort 1936 (LBC 1936) and the Simpson cohort. Brain imaging was used to examine the presence and severity of different markers of cSVD and self-report questionnaires were used to determine symptoms of depression and anxiety.

The thesis first examined whether cSVD was associated with symptoms of anxiety and depression. cSVD was not associated with symptoms of anxiety but the presence of some markers of cSVD were associated with more symptoms of depression. Secondly, this thesis examined relationships between birth and childhood factors and cSVD in adulthood. Birth factors such as increasing birth weight and increasing placental weight were associated with lower risk of cSVD. In childhood, increasing childhood IQ and more education was associated with decreased risk of cSVD in adulthood. Thirdly, this thesis examined associations between birth and childhood factors and symptoms of depression and anxiety in adulthood. In the Dutch Famine Birth Cohort people whose mothers were exposed to famine during pregnancy

reported more symptoms of anxiety and depression in adulthood. In STRADL and the LBC 1936 higher childhood IQ, more education and higher childhood SES were associated with lower symptoms of depression and anxiety.

Overall these results suggest that positive early life factors, particularly high childhood IQ may protect against cSVD and symptoms of depression and anxiety in older adulthood after the effect of age, sex, high blood pressure, smoking behaviour and adult SES are controlled for. The current findings are important because cSVD, depression and anxiety are serious health conditions and can increase risk of dementia and stroke. These findings may be used to inform changes in social policy and interventions to target those most at risk.

Declaration

I declare that the thesis has been composed by myself and that the work has not been submitted for any other degree or professional qualification. I confirm that the work submitted is my own, except where work has formed part of jointly authored publications has been included. My contribution and those of the other authors to this work have been explicitly indicated below. I confirm that appropriate credit has been given within this thesis where reference has been made to the work of others.

Some of the work presented in Chapter 1 was published in 2015 in *Current Epidemiology Reports* as “Early life risk factors for stroke and cognitive impairment” by Backhouse, EV. McHutchison CA., Cvoro V., Shenkin SD., Wardlaw JM. For this work I drafted the manuscript. Al other authors reviewed and edited the manuscript.

The work presented in Chapter 2 comprises of three papers published in 2017 and 2018. The work on early life risk factors and cSVD (Section 3.1) was published in Neurology as “Early life risk factors for cerebrovascular disease. A systematic review and meta-analysis” by Backhouse, EV. McHutchison CA., Cvoro V., Shenkin SD., Wardlaw JM. The work on early life factors and risk of stroke (Section 3.2) was published in *Epidemology* as “Education, socioeconomic status, and intelligence in childhood and stroke risk in later life. A meta-analysis” by McHutchison, CA, Backhouse, EV. Cvoro V., Shenkin SD., Wardlaw JM. The work on early life factors and post-stroke depression (section 3.3) was published in PLoS ONE as “Cognitive ability, education and socioeconomic status in childhood and risk of post-stroke depression: A systematic review and meta-analysis” by Backhouse, EV. McHutchison CA., Cvoro V., Shenkin SD., Wardlaw JM. For this work I carried out the systematic literature search, extracted the data, performed the meta-analysis, drafted the manuscripts for the papers published in *Neurology* and *PLoS ONE* and reviewed and edited the manuscript published in *Epidemiology*. CAM drew up the protocol, carried out the search, extracted data, performed the meta-analysis, drafted the manuscript published in Epidemiology and checked and edited the manuscripts published in *Neurology* and *PLoS ONE*. For all papers VC and SDS discussed the protocol and each, reviewed papers that were uncertain, advised on the meta-analysis, interpretation of the data and reviewed and edited the manuscript. VC helped obtain funding. JMW conceived the project, obtained funding, managed the project, designed the protocol and checked the search strategy, reviewed uncertain papers

and checked data, advised on the meta-analysis, interpretation of data and reviewed and edited the manuscript.

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Last but certainly not least I would like to thank my mum and dad for their endless love and support. Thank you for always believing in me, this thesis is dedicated to you.

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Abbreviations and definitions

Abbreviation	Meaning
ACDS	Aberdeen Child and Development Survey
ACONF	Aberdeen Children of the 1950s
AD	Alzheimer's disease
AH4	Alice Heim 4 test
AHC volume	Amygdala-hippocampal volume
β	Beta coefficient
CHD	Coronary heart disease
CI	Confidence interval
CMB	Cerebral microbleed
CSF	Cerebrospinal fluid
cSVD	Cerebral small vessel disease
CVD	Cerebrovascular disease
DSM-V	Diagnostic and Statistical Manual of the American Psychiatric Association fifth addition
EPVS	Enlarged perivascular spaces
FLAIR	Fluid-attenuated inversion recovery
GRE	Gradient echo
GS:SFHS	Generation Scotland Scottish Family Health study
GWAS	Genome-wide association study
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale- anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale- depression subscale

HPA axis	Hypothalamic pituitary adrenal axis
HR	Hazard ratio
ICV	Intracranial volume
IQ	Intelligent quotient
LBC 1936	Lothian Birth Cohort 1936
MD	Mean difference
MDD	Major depressive disorder
MMSE	Mini-mental state examination
MRI	Magnetic resonance imaging
NART	National Adult Reading Test
OR	Odds ratio
QIDS-16	Quick Inventor of Depressive Symptomology
SD	Standard deviation
SE	Standard error
SES	Socioeconomic status
SMS	Scottish Mental Survey
STRADL	Stratifying Resilience & Depression Longitudinally
SWI	Susceptibility-weighted imaging
WMH	White matter hyperintensity
χ	Chi-squared test

Increasing/ ~ed/ decreasing/~ed	As this study is cross sectional increased/decreased refers to higher/greater/more and lower/smaller/less respectively.

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1. Introduction

Globally the number of people over the age of 60 is expected to more than double, from 841 million people in 2015 to more than 2 billion by 2050 (United Nations, 2013). This is particularly evident in developed countries. In 2016 18% of the population of the United Kingdom (UK) were aged 65 and over and 2.4% were over the age of 85. The proportion of people over the age of 65 is expected to grow to 20.4% in the next 10 years and will reach 60% over the next 25 years. This is partly due to increased life expectancy which, in 2016, was 79.5 years for males and 83.1 years for females in the UK, compared to 71.1 years and 77.1 years in 1981 (Public Health England, 2017).

However, as life expectancy has risen, healthy life expectancy has increased more slowly. The association between age and health status is highly variable. A substantial proportion of older adults remain free of disease and disability. However data from longitudinal aging surveys suggests a clear trend of increasing disability with age. The increase in population aging has led to an increased prevalence of chronic non-communicable diseases in most high income countries. Globally these diseases are responsible for two thirds of deaths each year and are a large cause of morbidity and disability (Beaglehole et al., 2011). Improvements in acute hospital care mean that for many diseases associated with aging (i.e. stroke and dementia), the burden of disease arises more from disability than from mortality. Among the most common and burdensome disorders in people over the age of 60, measured using disability-adjusted life years (DALYs), are stroke (66.4 million DALYs), dementia (10.0 million DALYs) and major depressive disorder (7.5 million DALYs) (Prince et al., 2015).

Traditionally the risk of many of the most common chronic diseases, such as coronary artery disease and stroke, has been attributed to vascular risk factors and lifestyle behaviours in adulthood, such as smoking and hypertension. However it is recognised that factors from across the life course, including the prenatal environment and factors in childhood, can affect health and the risk of later disease (Barker, 2004). This has recently been recognised as a matter of international importance by the World Health Organisation (WHO), who identified investing in health through a life course approach as one of four priorities for policy action included in the Health 2020 framework (World Health Organization, 2013). Health 2020 is a health policy framework which aims to support government action across Europe to improve health and wellbeing. The aim

of the life course approach is to improve public health by targeting people at critical periods throughout their lifetime, including early life. Implementation of this strategy has resulted in key publications including guidance of maternal nutrition during pregnancy (Meija and Rezeberga, 2017, World Health Organisation, 2017).

The role of prenatal and early life factors has been well established for some diseases such as coronary heart disease (CHD) (Barker, 1995), but diseases such as cerebrovascular disease (CVD) and depression and anxiety in older adults have received less attention.

This aim of this thesis is to answer the question: are early life factors, measured at birth and in childhood, associated with cerebrovascular disase and symptoms of depression and anxiety in later life? To answer this question this Thesis will examine associations between early life factors and cerebrovascular disease, primarily as detected on neuroimaging, and depression and anxiety in systematic reviews and meta-analyses of the published literature, and in four de novo longitudinal cohort studies of participants aged 60-82 years.

This chapter will first discuss what is meant by cerebrovascular disease including the components of CVD on conventional magnet resonance imaging (MRI). It will then discuss the concept of late-life depression and how it is often associated with CVD. Finally it will discuss the current evidence for the role of early life factors in later disease burden, including the Developmental Origins of Health and Disease hypothesis.

1.1 Cerebrovascular disease

Cerebrovascular disease (CVD) is a broad term used to describe pathophysiological changes in the brain resulting from abnormalities in the brain's vasculature. CVD is common at older ages and causes a substantial proportion of dementias. CVD can present as clinical stroke but can also result in subclinical brain changes detected on neuroimaging (Wardlaw et al., 2013).

Stroke is a clinical diagnosis of a sudden onset of a neurological deficit caused by interruption of the brain's blood supply. It is defined by the WHO as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin" (WHO Monica Project Principal Investigators). 20% of strokes are

haemorrhagic and 80% are ischaemic. Haemorrhagic stroke occurs when a blood vessel ruptures in the subarachnoid space (5%) or intracerebral tissue (15%). This leads to bleeding in the brain and increasing intracranial pressure, which can result in severe neurologic symptoms and death. Ischaemic stroke on the other hand, is caused by a decrease in cerebral blood flow which if not restored can result in cerebral infarction. If blood flow is restored to ischaemic tissue before a significant infarction develops, the resulting neurologic symptoms may be transient and brain tissue can fully recover. A 'transient ischaemic attack (TIA)' refers to signs and symptoms that resolve within 24 hours. If blood flow is not restored for several minutes or hours this can result in permanent brain infarction. Ischaemic stroke may be caused by processes intrinsic to the vessel as seen in atherosclerosis, or may originate remotely, as occurs when an embolus from the heart or extracranial circulation lodges in an intracranial vessel. 75% of ischemic strokes are atherothromboembolic or cardiac. The remaining 25% are small vessel or 'lacunar' strokes caused by cerebral small vessel disease (cSVD) (Adams et al., 1993).

A lacunar stroke is defined as a small (usually <15mm diameter) subcortical infarct located in the white matter, basal ganglia, pons or brainstem with a lacunar clinical syndrome such as pure motor stroke/hemiparesis (Wardlaw et al., 2013). Lacunar infarcts result from an abnormality in a single penetrating artery of the brain and are visible as round or ovoid areas of hyperintense signal on diffusion-weighted imaging (DWI), T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging (Wardlaw et al., 2013). However it has been shown that nearly one third of patients with symptomatic lacunar stroke syndromes do not have a relevant lesion on DWI-MRI (Makin et al., 2015). This indicates that MRI may not be fully sensitive in the detection of such lesions and suggests that negative DWI or MRI findings should not exclude stroke diagnosis.

Conversely, recent small subcortical infarcts can also occur with no acute stroke symptoms and are referred to as silent cerebral infarcts or sometimes as 'silent' strokes. Unfortunately, the term 'silent stroke' is unhelpful since it implies a mechanism that may not be relevant. Hence in this Thesis, unless unavoidable, will refer to the lesions by their specific names. Lacunes are one manifestation of a spectrum of radiological markers of cSVD, which are often clinically 'silent', but play a crucial role in stroke, dementia and ageing. These features are described in the next section.

1.1.1 Clinically 'silent' cerebral small vessel disease

Cerebral small vessel disease (cSVD) refers to a syndrome of clinical and neuroimaging findings in the white and subcortical grey matter which result from pathologies in the small perforating cerebral arterioles, capillaries and venules. These small vessels cannot be easily visualised in vivo, or by current standard neuroimaging techniques. Therefore vascular lesions which can be visualised on MRI, and are thought to result from these pathological changes in the small vessels, are used as markers of cSVD. cSVD features detected on conventional MRI include, recent small subcortical ('lacunar') infarcts, white matter hyperintensities (WMH), lacunes, cerebral micro-bleeds (CMBs), enlarged perivascular spaces (EPVS) and atrophy. These are displayed in Figure 1. Although often clinically silent, these features create an enormous health burden, leading to significant neurologic and cognitive decline. cSVD is responsible for a fifth of all strokes (Sudlow and Warlow, 1997), is the commonest vascular cause of dementia (Hachinski, 2007a) and is associated with psychiatric and physical disabilities (Wardlaw et al., 2013, Debette and Markus, 2010). Notably, WMH the commonest feature of small vessel disease, treble the risk of stroke and double the risk of dementia and death (Debette and Markus, 2010).

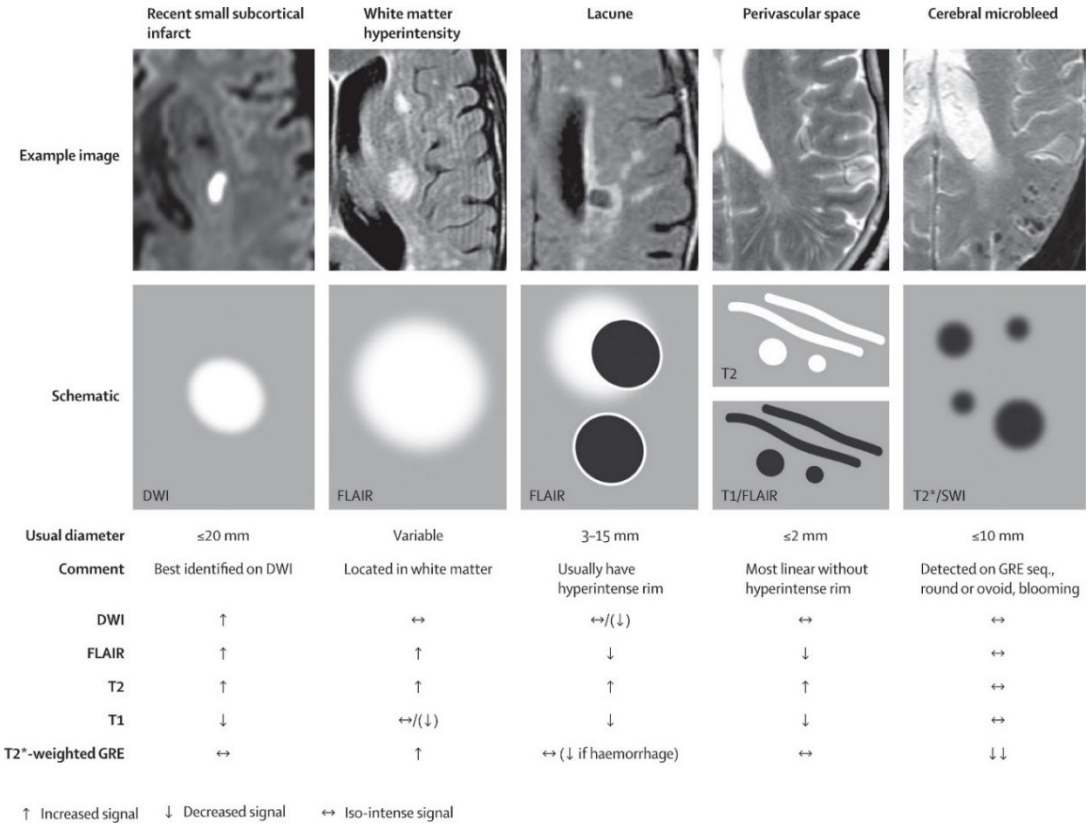


Figure 1.1: STRIVE, STandards for Reporting and Imaging of Small Vessel Disease: example findings (upper), schematic representation (middle) and a summary of imaging characteristics (lower) of MRI features for changes related to small vessel disease DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; SWI, susceptibility-weighted imaging; GRE, gradient-recalled echo. Reproduced from Wardlaw et al Lancet Neurol 2013; 12:822-38 with permission from the publishers Elsevier Ltd (license number 4316990803404 dated 27 March 2018).

1.1.1.1 White matter hyperintensities (WMH)

WMH of assumed vascular origin are visible as areas of increased signal on T2-weighted or FLAIR MR imaging. They appear bilaterally, and usually symmetrically, in the periventricular and deep white matter, including the pons, brainstem and cerebellum, and also in deep grey matter such as the basal ganglia and thalamus. The underlying pathology of WMHs is unclear. However findings in regions of WMH include increased interstitial fluid (Muñoz Maniega et al., 2017) and the traditional pathological reports of axonal loss, demyelination and rarefaction presumed to be caused by chronic ischaemia seen in end stage disease (Prins and Scheltens, 2015). Depending on their stage in development and severity, WMHs can be focal or

multifocal becoming confluent as they become more extensive. Multiple mechanisms underlying WMH have been proposed including chronic hypoperfusion (now largely disproved (Shi et al., 2016)), dysfunction of blood-brain barrier (Wardlaw et al., 2003, Simpson et al., 2007), inflammation and amyloid angiopathy (Gouw et al., 2011). WMHs predict future stroke (Yamauchi et al., 2002) and are associated with decline in verbal IQ (Garde et al., 2005) and executive function (Debette and Markus, 2010) and dementia, particularly vascular dementia and Alzheimer's disease (AD) (Prins and Scheltens, 2015). The prevalence and severity of WMH increase with age. They are also more common in people with vascular risk factors, particularly hypertension, and are more extensive in patients with acute lacunar stroke than in patients with other stroke subtypes (Rost et al., 2010) . The exact prevalence of WMHs is hard to determine due to differences in imaging techniques, ratings used and populations studied. Two population based studies, the Cardiovascular Health Study and Rotterdam Scan study reported that the prevalence of any WMHs in participants over the age of 60 years was 96% and 95% respectively (Longstreth et al., 1996, de Leeuw et al., 2001).

1.1.1.2 Lacunes

Lacunes of presumed vascular origin are round or ovoid subcortical cerebrospinal fluid (CSF)-filled cavities found in the deep grey or white matter. They have a diameter of 3-15 mm on brain MRI or autopsy. Lesions less than 3 mm are more likely to be perivascular spaces and lesions larger than 15 mm are more likely to be caused by mechanisms other than cSVD (Valdés Hernández et al., 2013b, Valdés Hernández et al., 2013a). Lacunes appear on FLAIR images as a hypointense CSF hole often, but not always, surrounded by a hyperintese rim. This rim can help distinguish them from PVS but PVS are also found in areas of extensive WMH. Lacunes can result from previous small subcortical lacunar infarcts, either symptomatic or silent, which shrink and leave small cavities (Wardlaw et al., 2013, Vermeer et al., 2007). In some cases acute lacunar infarcts do not cavitate and either appear as areas of WMH or disappear completely. A small proportion of lacunes are due to a small haemorrhage (Wardlaw et al., 2013). In the general elderly population the prevalence of lacunes ranges from 8% to 28% (mean age 59-75) (Vermeer et al., 2007).

1.1.1.3 Enlarged perivascular spaces (EPVS)

Enlarged perivascular spaces (EPVS) are fluid filled spaces that surround cerebral microvessels and follow the course of the vessel from the subarachnoid space through the brain parenchyma (Braffman et al., 1988). EPVS are microscopic and normally not visible on conventional neuroimaging however when enlarged they are visible on T2 weighted MRI, most frequent in the basal ganglia and centrum semiovale, with a signal intensity similar to CSF. They appear linear when imaged parallel to the course of the vessel or punctuate with a diameter of <3mm when imaged perpendicular to the course of the vessel. Perivascular spaces are conduits for drainage of interstitial fluid (ISF) from the brain and their visibility on MRI may be associated with altered drainage of ISF (Abbott, 2004, Weller et al., 2009, Xie et al., 2013). EPVS are markers of inflammation or blood brain barrier (BBB) dysfunction. For example in patients with multiple sclerosis EPVS are found in and around active lesions associated with inflammation (Wuerfel et al., 2008). EPVS were associated with increased BBB permeability and inflammation in cSVD (Wardlaw et al., 2009).The clinical significance of EPVS remains unclear. Although small amounts of EPVS are found in healthy adults of any age, large numbers are associated with increasing age, impaired cognitive function and depression (Zhu et al., 2010, MacLullich et al., 2004, Patankar et al., 2007). Furthermore an association with cerebral cSVD is suggested by their greater frequency in patients with other features of cSVD (Zhu et al., 2010, Doubal et al., 2010), in those with vascular dementia as opposed to Alzheimer's disease (Patankar et al., 2005), and their association with lacunar stroke subtype (Doubal et al., 2010, Potter et al., 2015) and hypertension (Zhu et al., 2010).

1.1.1.4 Cerebral microbleeds

Cerebral microbleeds are visible on T2* or susceptibility-weight imaging (SWI) as small punctuate hypointense areas up to 10mm in diameter. They are thought to represent haemosiderin-laden macrophages close to a structurally abnormal vessel (Shoamanesh et al., 2011, Gouw et al., 2011). Some studies suggest that two main forms of vasculopathies are associated with microbleeds in the aging brain: deep microbleeds located in the basal ganglia, thalamus, brainstem and cerebellum are attributed to cerebral hypertensive vasculopathy and lobar microbleeds in the cortical-subcortical regions of brain are attributed to amyloid angiopathy (Greenberg et al., 2009). However this is over simplistic and reflects small studies in specialist centres

since lobar microbeads can occur in hypertensive individuals and deep microbleeds occur in cerebral angiopathy, so these distributions should not be interpreted literally. Microbleeds are occasionally seen in healthy adults and are often asymptomatic, however prevalence increases with age (Poels et al., 2010) and they are associated with lacunar stroke, WMHs and vascular risk factors (Gouw et al., 2011, Wardlaw et al., 2006). They are also associated with cognitive impairment and dementia (Cordonnier et al., 2006, Martinez-Ramirez et al., 2014). The prevalence of microbleeds varies depending on the population studied. Population-based studies have reported on microbleed prevalence in healthy older individuals as 11.1-15.3% (mean age 60.3 and 76 years) (Sveinbjornsdottir et al., 2008, Poels et al., 2010). A higher prevalence is reported in patient populations; 33.5% in ischaemic stroke patients, 60.4% in non-traumatic intracerebral haemorrhage (Cordonnier et al., 2007) and 17-46% in those with cognitive decline or dementia (Cordonnier et al., 2006).

1.1.1.5 Brain atrophy

Brain atrophy is a common finding on MRI. Most people in the general older population have some degree of cerebral atrophy but the extent varies between individuals. In community dwelling older adults mean total brain volume loss was estimated as 0.64% per year at age 73-76 years (Ritchie et al., 2015). Reduced cortical brain volume can affect grey and white matter, resulting in increased CSF surrounding the brain and in the lateral ventricles. Whether atrophy affects mainly the white or grey matter is unclear. Some studies suggest that brain atrophy in normal aging predominantly affects the grey matter, particularly the frontal and parietal lobes (Resnick et al., 2003). One meta-analysis showed that declines in grey matter were stronger than white matter across the lifespan (Walhovd et al., 2011). Other studies have suggested that declining white matter is more evident in the oldest participants (>70 years), and that despite its late onset, white matter loss is more rapid than grey matter loss and will eventually exceed it (Jernigan and Gamst, 2005, Jernigan et al., 2001). The pathological changes of atrophy are heterogeneous and may include, atherosclerosis, cortical thinning and subclinical vascular disease (Black et al., 2009, Jagust et al., 2008). White matter damage due to underlying small vessel disease may lead to loss of myelin, axons and oligodendrocytes and other glial cells in the subcortical white matter (Appelman et al., 2009). Alternatively cortical microinfarcts may cause cortical grey matter atrophy (Smith et al., 2012).

Brain atrophy, particularly in the hippocampus and entorhinal cortex, has been associated with neurological diseases such as Alzheimer's disease (Braak and Braak, 1991, Frisoni et al., 2010, Delacourte et al., 1999), and atrophy has been shown to predict conversion to Alzheimer's disease in those with mild cognitive impairment (Frisoni et al., 2010). Atrophy may not always be considered as a marker of cSVD. However in healthy adults increased cortical atrophy is often seen in patients with other markers of cSVD and is associated with vascular risk factors (Appelman et al., 2009, Firbank et al., 2007). Previous studies have shown that WMH burden correlated with total grey matter atrophy (Aribisala et al., 2013, Wang et al., 2014b), and longitudinal studies have shown a relationship between baseline WMH and lacunar infarcts and brain atrophy over time (Schmidt et al., 2005), independent of vascular risk factors (Kloppenborg et al., 2012, Dickie et al., 2015). Furthermore some studies report an association between presence and severity of cSVD and brain atrophy. Lambert et al (2016) found that progression of WMH was associated with increased cortical grey matter atrophy in the medial-frontal, orbital-frontal, parietal and occipital regions. However Dickie et al showed that the progression of WMH and cortical atrophy was not linked (Dickie et al., 2015). Lambert (2016) also found that increased global rates of grey matter atrophy were associated with increased WMH growth in the frontal and parietal regions (Lambert et al., 2016). Given these potential associations, atrophy is an important measure in imaging studies done to assess cSVD.

1.1.2 Cognitive impairment and dementia

Cerebrovascular disease has been identified as a major cause of acquired cognitive impairment and dementia including vascular dementia (VaD) and Alzheimer's disease (AD) (Snyder et al., 2015, Hachinski et al., 2006). Vascular contributions to cognitive impairment and dementia (VCID) have emerged as a leading priority in dementia research (Snyder et al., 2015, Corriveau et al., 2016). VCID is a broad term used that emphases the heterogeneous group of cognitive disorders associated with vascular disease, ranging from mild to severe cognitive impairment to vascular dementia (VaD) (Moorhouse and Rockwood, 2008, Corriveau et al., 2016). Vascular insults which may lead to cognitive impairment or dementia are diverse and include clinical or silent stroke, TIA, cerebral amyloid angiopathy (CAA), cSVD and brain atrophy (Snyder et al., 2015). Lacunar infarcts and ischaemic white matter lesions are the most common type of cSVD lesion associated VCID. Monogenic disorders such as Cerebral

Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) also lead to younger onset vascular cognitive impairment or dementia (Chabriat et al., 2009).

Considerable cerebrovascular pathology is also evident in AD including cSVD and brain atrophy (Sperling et al., 2011) and vascular risk factors are also risk factors for AD. Furthermore recent findings indicate that vascular changes and degenerative pathologies linked to AD interact suggesting a synergistic effect on cognitive decline (Nation et al., 2015, Iliff et al., 2014).

Longitudinal studies of healthy older adults have provided clear evidence that cSVD and brain volume are two of the neuroanatomical bases of normal cognitive aging. Markers of cSVD, particularly WMHs, are associated with lower cognitive abilities and steeper cognitive decline (Prins and Scheltens, 2015, Kloppenborg et al., 2014). Meta-analysis of 37 studies of older adults (mean age >50 in all studies) without dementia found that the prevalence of WMHs was associated with small but robust reductions in cognitive functioning across all cognitive domains examined (Kloppenborg et al., 2014). These associations were observed in cross sectional studies (23 studies) and longitudinal studies (14 studies). In those examining WMHs and cognitive decline over time associations were most pronounced for general intelligence (r= -0.31) and executive functioning (r= -0.32) (Kloppenborg et al., 2014). All of the studies included adjusted for age, sex and education level, however few adjusted for additional factors such as vascular risk factors.

Total brain volume and specific brain regions such as grey and white matter have also consistently been shown to correlated with cognition in adulthood (Grazioplene et al., 2015, Arvanitakis et al., 2016, Jokinen et al., 2012, Kramer et al., 2007).

Several mechanisms have been proposed for the association between cSVD and cognitive decline and dementia and it is likely that multiple mechanisms interact. Information processing speed and executive function are associated with white matter integrity (Penke et al., 2010). Therefore small vessel disease lesions could damage subcortical neural networks directly, disrupting neural transmission and connectivity and resulting in decreased processing speed and executive function. Alternatively cSVD may indirectly lead to cognitive decline through incident stroke (Vermeer et al., 2003). cSVD could reflect vascular risk factors common to both cSVD and cognitive impairment, or could indicate poor vascular health which may impair cognition (Prins

and Scheltens, 2015). However several studies have adjusted for vascular risk factors and stroke and have reported similar associations suggesting that shared vascular risk factors is not the main mechanism.

1.1.3 Risk factors and treatment for cSVD

Features of cSVD are associated with several common vascular risk factors, particularly hypertension (Dufouil et al., 2001, Godin et al., 2011, Marcus et al., 2011, Gottesman et al., 2010), but also hypercholesterolemia, smoking (van Dijk et al., 2008, Gons et al., 2011), and diabetes mellitus and salt intake (Heye et al., 2016). Hypertension is more prevalent in patients with WMH and high blood pressure is associated with more severe WMH (van Dijk et al., 2004) and more progression of WMH over time (Dufouil et al., 2001, Gottesman et al., 2010, Godin et al., 2011, de Leeuw et al., 2002). One large study of 10 European cohorts (n=1625, age 65-75 years) found that higher concurrent blood pressure and blood pressure measured in the years previously were associated with an increased risk of severe WMH (van Dijk et al., 2004). Blood pressure has also been associated with total cSVD burden in two studies (Staals et al., 2014, Klarenbeek et al., 2013). Other risk factors for cSVD include lifestyle factors such as smoking, diet including salt intake and exercise. Current smoking is associated with WMH progression (van Dijk et al., 2008, Debette et al., 2011), reduced microstructural integrity of the white matter (Gons et al., 2011), higher total cSVD burden (Staals et al., 2014) and higher global brain atrophy (Debette et al., 2011). Higher dietary salt intake is associated with increased WMH burden partly through increasing blood pressure and via a direct effect on the endothelium (Heye et al., 2016). Physical activity was associated with better white matter integrity, lower WMH burden and less cerebral atrophy in community dwelling adults in their early 70s (Gow et al., 2012) . However the direction of causation is unclear and physical activity could be a proxy for good general health (Gow et al., 2012).

These modifiable risk factors therefore offer potential therapeutic targets. Successful treatments for cSVD aim to reduce WMH progression and development of new lacunes, microbleeds or brain atrophy and clinical manifestations such as stroke, cognitive decline and dementia. It has been hoped that cSVD29h prevention could be achieved through pharmacological treatments such as antihypertensive medications, statins and antiplatets (Bath and Wardlaw, 2015) or through changes in lifestyle, although the results of trials of blood pressure lowering have so far been very

disappointing and dual versus single antiplatelet drugs were hazardous (The SPS3 Study Group, 2013, Benavente et al., 2012).

The lack of benefit from antihypertensive agents so far may be understood if one considered the relationship between vascular risk factors and cSVD which is complex. One study found that vascular risk factors combined only explained 2% of the variance in WMH (Wardlaw et al., 2014). While observational studies have shown that blood pressure management may reduce WMH progression (Dufouil et al., 2001, Godin et al., 2011), in randomised control trials (RCTs), antihypertensive treatment had little (Dufouil et al., 2005) (n=192, mean age 60) or no effect (The SPS3 Study Group, 2013, Weber et al., 2012) (n= 771 mean age 65). Similarly, studies investigating the effect of statins on WMH progression have produced contradictory findings. One study found that pravastatin did not prevent WMH progression after 33 months (ten Dam et al., 2005). Another study found that treatment with simvastatin was associated with reduced WMH volume after two years but only in those with severe WMH burden at baseline. No association was found in those with mild baseline WMH burden (Mok et al., 2009).

In the SPS3 trial, a large randomised control trial (RCT) of patients with lacunar stroke, blood pressure reduction not only did not prevent recurrent stroke, it also failed to prevent cognitive decline, and dual antiplatelet drugs were both hazardous and did not prevent cognitive decline or stroke (Pearce et al., 2014, The SPS3 Study Group, 2013, Benavente et al., 2012). Furthermore the SPS3 trial also found that long term dual antiplatelet treatment significantly increased the risk of bleeding after lacunar stroke without reducing the risk of stroke recurrence (Benavente et al., 2012).

The PRoFESS study also found no effect of dual antiplatelet therapy on cognition (Diener et al., 2008).

Secondary prevention lifestyle interventions such as physical activity and improving diet, may have more effect on improved health outcomes such as blood pressure, BMI and cholesterol levels and in turn on reducing WMH progression (Ngandu et al., 2015). What is less clear is whether these interventions reduce stroke reoccurrence (Lawrence et al., 2012).

Management of traditional vascular risk factors should still be encouraged however clearly a new approach is needed. Possible targets for future prevention and treatment of cSVD and cognitive impairment include treatments to reduce small

vessel endothelial damage to prevent progressive BBB breakdown and brain injury (Wardlaw et al., 2017, Bath and Wardlaw, 2015). BBB dysfunction is common in lacunar stroke and in those with severe WMHs and may contribute to dementia associated with cSVD (Wardlaw et al., 2013, Wardlaw et al., 2017). Experimental studies have shown that nitric oxide/cyclic guanylate monophosphate (cGMP) and prostacyclin/cyclic AMP (cAMP) modulators can improve BBB integrity and are a promising therapeutic target (Bath and Wardlaw, 2015). However more clinical trials are needed (Blair et al., 2017)

1.1 Late-life depression

Depressive disorders are a serious public health problem among older adults. They are a leading cause of disability worldwide leading to more years lived with disability than any other disease (Alexopoulos and Kelly, 2009). Late-life depression refers to depressive syndromes defined in the American Psychiatric Association's Diagnostic and Statistical Manual (DSM-V) (American Psychiatric Association, 2013) and the International Classification of Disease (ICD-10) (World Health Organization, 1992) that occur in adults over the age of 60 years. Mood disorders can present as major depressive disorder (MDD) or subthreshold depression that does not meet the full criteria for MDD.

MDD is less prevalent in healthy community dwelling older adults than in younger adult populations (Jorm, 2000). However a significant proportion of adults experience some type of depression in older adulthood. In community based studies of individuals over the age of 60, estimated prevalence of MDD varies between 1.6% and 5.4% (Park et al., 2010, Sjöberg et al., 2017). Rates of depression rise with increasing medical morbidity (Sjöberg et al., 2017). In primary care settings 5-10% of adults over the age of 60 present with MDD (Lyness et al., 1999a) and prevalence rises to 37% after critical care hospitalisations (Jackson et al., 2014b). In long term care facilities up to 50% of older adults (>65 years) report symptoms of depression (Hoover et al., 2010). However older people often underreport the severity and presence of depressive symptoms (Alexopoulos, 2005) and therefore the prevalence of depression may be higher than the figures suggest.

There is increasing recognition of subthreshold forms of depression, which encompasses minor depression, subsyndromal depression, dysthymia and brief recurrent depressive disorder. Subthreshold depression is at least 2-3 times more

prevalent in older adults than MDD. Like MDD, prevalence is lower in community settings (approximately 8-16%) than in primary care and highest in nursing homes (up to 61%) (Meeks et al., 2011). Subsyndromal depression is a major risk factor for comorbid anxiety disorder and new-onset MDD and should not be overlooked (Laborde-Lahoz et al., 2015, Meeks et al., 2011). A review of 181 studies of late-life subthreshold depression found that approximately 8-10% of older adults with subthreshold depression will develop clinical depression each year (Meeks et al., 2011).

1.1.1 Diagnosis of late-life depression

There is no specific diagnostic criteria for late-life depression. It is diagnosed using the same criteria as that used for MDD in younger adults, mainly the DSM-V (American Psychiatric Association, 2013) or ICD-10 (World Health Organization, 1992). The diagnostic criteria for MDD in the DSM-V require the presence of one or both of depressed mood and anhedonia, along with five or more additional symptoms: significant weight change (5%) or change in appetite, changes in sleep, psychomotor agitation or retardation, fatigue, inappropriate feelings of guilt or worthlessness, diminished ability to concentrate or make decisions and recurrent thoughts of death or suicidal ideation. These must be present over a two-week period. Identifying depression in older adults can be often challenging in light of coexisting physical comorbidities, and age-related physiological changes. There are often subtle differences in clinical presentation of depression by age which are not captured in standard diagnostic criteria. For example, low mood and/or sadness may be less common in depression with a later age of onset compared to depression earlier in life and symptoms such as irritability, psychomotor retardation, anxiety and multiple and non-specific somatic symptoms may be more common (Fiske et al., 2009).

Subthreshold forms of depression are characterised by clinically relevant depressive symptoms that do not meet the full criteria for MDD. According to the Appendix of the DSM-V minor depression is diagnosed by the presence of 2-4 symptoms of depression one of which must be depressed mood or anhedonia. However, research has shown that this criteria does not fully capture symptoms of other forms of subthreshold depression, for which there is currently no universally accepted method of diagnosis (Meeks et al., 2011, Rodríguez et al., 2012). The presence of depressed mood or anhedonia with one or more additional symptom of MDD are often used as

criteria. Alternatively clinically relevant symptoms can be ascertained using cut off scores on self-rating depression scales.

Both subthreshold depression and late -life depression are associated with impairments in physical functioning and activities of daily living (ADLs), lower quality of life , poorer self-rated health and greater uses of health services (Rodríguez et al., 2012).

Older adults with depression commonly exhibit problems with cognition, particularly deficits in memory, processing speed and executive function (Alexopoulos et al., 1997b, Butters et al., 2004). Executive functions involve numerous domains including, but not limited to, control mechanisms that modulate aspects of emotion and cognition (Diamond, 2013). Disruption of these processes is associated with poor clinical outcomes of late-life depression (Pimontel et al., 2016, Alexopoulos et al., 2004). Coexisting mood symptoms are also common in cognitive disorders and dementia. The prevalence of MDD is about 17% in patients with AD (Wragg and Jeste, 1989) and is even higher in those with subcortical dementias (Panza et al., 2010). Some studies (Jajodia and Borders, 2011, Vinkers et al., 2004) suggest older adults may develop depressive symptoms in reaction to experiencing cognitive decline. Other studies suggest that depression is a risk factor for cognitive decline. A meta-analysis of 20 studies found that depression is associated with a 2-fold increased risk of Alzheimer's disease (Ownby et al., 2006). On the other hand it has been argued that depression is a prodrome of dementia and that both are symptoms of a shared underlying neurodegenerative process (Panza et al., 2010). A recent 28 year follow up cohort study (Singh-Manoux et al., 2017) found that depressive symptoms in late life were associated with a higher risk of dementia. However there was no association between depressive symptoms in midlife and dementia, even when depression was chronic or recurring. These findings support the idea that depressive symptoms may represent a prodrome of dementia rather than a risk factor and suggest that depressive symptoms can accompany insidious cognitive decline years before the clinical manifestation of dementia.

1.2.1 Aetiology of late-life depression

The aetiology of late-life depression is thought to be multifactorial, involving complex interactions of biological, genetic and psychosocial factors. There is substantial heterogeneity in the biological factors that influence the risk of developing depression

in older adults, but one of the best studied is the role of vascular disease which can result in post-stroke depression and vascular depression (Alexopoulos et al., 1997b, Gaete and Bogousslavsky, 2008). These will be described below.

1.2.1.2 Post-stroke depression

Post-stroke depression develops after cerebral infarct or haemorrhage. Approximately 31% of patients experience depression during the first 5 years following a stroke (Hackett and Pickles, 2014) making it the most common post-stroke neuropsychiatric disturbance. People with post-stroke depression experience greater impairment, including worse cognitive impairment, more substantial reductions in activities of daily living and increased mortality compared to non-depressed stroke patients (Robinson and Jorge, 2016). Furthermore depression can severely impair physical rehabilitation and recovery (Robinson and Jorge, 2016). The aetiology of post stroke depression is still unclear. Some researchers propose that the primary mechanism linking stroke and depression is biological in which brain damage caused by ischaemic lesions disrupt neural circuits involved in mood regulation. Others propose that post-stroke depression is caused by dysfunctional psychosocial adjustment following the stroke. It is likely that post-stroke depression is of multifactorial origin and a combination of biological and psychosocial mechanisms.

1.2.1.3 Vascular depression

In contrast to depression in younger adults, late life depression is associated with cerebrovascular comorbidities which may be evident years before the onset of depressive symptoms. In 1997 Alexopoulous coined the term ‘vascular depression’ and suggested that “cerebrovascular disease may predispose, precipitate or perpetuate some geriatric depressive syndromes” (Alexopoulos et al., 1997a). This was based on observations of high rates of depression in patients with vascular risk factors such as cardiovascular disease, hypertension and diabetes, the frequent occurrence of depression in stroke patients and those with silent stroke and WMHs, and the lower frequency of a family history of depression in geriatric depression (Alexopoulos et al., 1997a). Vascular depression is the most common subtype of late life depression and presents clinically with comorbid deficits in executive function, lack of insight, psychomotor retardation and cognitive dysfunction and disability, which are disproportionate to the depression severity and greater than in those who are depressed but do not have vascular disease (Alexopoulos et al., 1997b). Cognitive

functions which are most affected in vascular depression are verbal fluency and object naming (Alexopoulos et al., 1997b, Krishnan et al., 1997).

Another core characteristic of vascular depression was proposed by Krishnan et al (1997) who suggested an MRI-based definition which required evidence of vascular changes on neuroimaging (Krishnan et al., 1997). Late-life depression is associated with different brain pathologies including several markers of cSVD (van Agtmaal et al., 2017), but the most prominent MRI characteristic is WMHs. Older adults with late-life depression consistently have greater WMH severity and higher WMH volume than non-depressed older adults or younger individuals with depression (Herrmann et al., 2008, van Agtmaal et al., 2017). A recent meta-analysis of 46 studies found that higher WMH burden (measured by severity and volume) was associated with increased risk of incident late-life depression in 38 cross sectional studies (OR 1.29 95% CI 1.19-1.39) and 8 longitudinal studies (OR 1.18 95% CI 1.08-1.28) (van Agtmaal et al., 2017). Among older adults with depression, greater WMH severity is associated with greater depression severity (Firbank et al., 2005), poorer cognitive function (Sheline et al., 2008) and poorer outcomes (Grool et al., 2013, Park et al., 2015). Longitudinal studies of participants free of depression at baseline suggest that WMHs precede incident depression and support a causal rather than correlative relationship in older adults (Qiu et al., 2017, Tully et al., 2017). One longitudinal study found that those with WMHs at baseline had a fourfold increased risk of developing depressive symptoms 6 years later than those with no vascular disease at baseline (Qiu et al., 2017).

Late-life depression has been associated with other markers of cSVD including lacunes, microbleeds, silent brain infarcts (van Agtmaal et al., 2017) and EPVS (Greenstein et al., 2010), as well as grey matter volume reductions in the fronto-striato-limbic region (Sexton et al., 2013a, Tudorascu et al., 2014, Du et al., 2014). However these features have received less attention that WMHs.

There are various mechanisms by which vascular disease may lead to the development and persistence of depression (Taylor et al., 2013). Vascular disease may contribute to late-life depression by disrupting white matter tracts in key frontal-subcortical circuits involved in mood regulation and cognition (Alexopoulos et al., 1997a, Krishnan et al., 1997). According to Alexopoulos (2005) this may occur as a result of a single localised lesion or through the accumulation of lesions which increase vulnerability to, or result in, problems with cognition and mood once reaching

a certain threshold (Alexopoulos, 2005). Several small mostly single centre imaging studies examining WMHs volumes in older adults have found that, compared to non-depressed older adults, those with depression have more WMHs located in the frontal and temporal lobes (Godin et al., 2008, Taylor et al., 2003, Firbank et al., 2004, O'Brien et al., 2006), and in specific fibre tracts of the cingulate bundle, uncinated fasciculus and superior longitudinal fasciculus (Sheline et al., 2008, Dalby et al., 2010, Taylor et al., 2013). It is possible that greater severity of WMHs in these tracts, which underlie brain regions associated with cognitive and emotion function, may be associated with more severe depression and greater executive dysfunction (Sheline et al., 2008, Smith et al., 2011, Dalby et al., 2010). However, this hypothesis remains to be tested in large, diverse and clinically relevant cohorts.

Global WMHs can disrupt local white matter tracts but may also be an indicator of global white matter integrity. WMHs have reduced white matter integrity, indicated by lower fractional anisotropy and higher mean diffusivity, compared with normal appearing white matter (Muñoz Maniega et al., 2015). In turn the integrity of normal appearing white matter is associated with the severity of WMHs, even in those with low WMH burden (Muñoz Maniega et al., 2015), suggesting that total WMH burden may be indicative of white matter damage that is not visible on conventional MRI.

Other biological mechanisms that have been proposed linking vascular disease and depression include cerebral hypoperfusion (Taylor et al., 2013), abnormal inflammatory responses (Kim et al., 2018, Leonard and Maes, 2012), deficits in neurotransmitter signalling (Savitz et al., 2009), and common genetic factors (Gilbody et al., 2007, Hickie et al., 2001, Scherrer et al., 2003) all of which remain to be tested.

1.2.1.4 Psychosocial factors

Psychosocial factors contributing to late life depression may include stressful life events such as death of a spouse or loved one and ongoing difficulties such as medical illness, disability and functional decline. According to a meta-analysis of 25 studies negative life events appear to have a modest but significant association with depression in older adults, however this did not take into account vascular disease (Kraaij et al., 2002). The chronicity and perceived uncontrollability of these events may lead to feelings of helplessness and/or hopelessness which may result in symptoms of depression (Aziz and Steffens, 2013). For example external locus of control orientation, an aspect of coping, is associated with health related quality of life

(Helvik et al., 2016), depressive symptoms and diagnosis of depression (Bjørkløf et al., 2018) in older adults. External locus of control refers to the perception that outside forces, luck or coincidence are responsible for outcomes in one's life. On the other hand internal locus of control is the belief that events result from one's own actions and control (Rotter, 1966). Neuroticism may interact with stressful life events to increase risk of depression. One study found that both were associated with higher risk of depression however stressful life events did not increase risk without the presence of neuroticism whereas neuroticism increased risk even without stressful life events (Ormel et al., 2001).

Social support has a strong impact on healthy and quality of life in older adults. Both loneliness, the subjective appraisal of social isolation, and an insufficient social network, an objective marker of social isolation, are associated with depression in older adults (Golden et al., 2009, Luanaigh and Lawlor, 2008). Perceived social support has been shown to be a stronger predictor of late life depressive symptoms than other objective measures of network relationships.

1.2.2 Treatment for late-life depression

The treatment of depression in older adults has been set out in various guidelines (Pilling et al., 2009, Stahl et al., 2017), in which the emphasis is on pharmacological treatments (tricyclic anti-depressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors) and/or psychological therapy (Cognitive Behavioural Therapy (CBT), behavioural activation treatments, interpersonal psychotherapy and problem-solving treatments).

Assessing the efficacy of pharmacological treatments in older adults is difficult as double-blind, placebo-controlled trials are largely conducted in younger adults and often exclude those over the age of 65. Two meta-analyses found that pharmacological treatments are superior to placebo in those over the age of 55 (15 studies) or 60 (13 studies) (Tedeschini et al., 2011, Nelson et al., 2008). However when confined to studies of adults over the age of 65, the efficacy of antidepressants is largely reduced, and is much lower than in adult MDD (Tedeschini et al., 2011). This may be due to several factors including the presence of executive dysfunction, WMHs, medical comorbidity, chronicity and under treatment, all of which are common in late life depression and are associated with poorer treatment response. Furthermore older adults may be particularly vulnerable to the adverse side effects

associated with antidepressant medication, which can compromise compliance and effectiveness of treatment (Coupland et al., 2011).

Evidence suggests that psychotherapy is efficacious in older depressed adults (*d*= 0.72 95% CI 0.59-0.85) (Cuijpers et al., 2011) and most guidelines advocate the additional benefit of supporting antidepressant medication with psychosocial interventions (Charney et al., 2003, Reynolds et al., 1999, Wilson et al., 2008). The effects of psychotherapy are comparable across different types of therapy, and for depression diagnosed using diagnostic rating criteria or self-report questionnaire (Cuijpers et al., 2006). Furthermore psychotherapy in older adults is just as effective as in younger adults (Cuijpers et al., 2009). However the available evidence of the efficacy of psychotherapy for older adults with severe depression is limited to younger older adults (<70 years) with mild to moderate depression. Further research is needed in more severe forms of depression in the older old.

Treatment resistant depression affects up to one third of patients with late-life depression (Mulsant and Pollock, 1998) possibly due to high levels of vascular disease (Aizenstein et al. 2014). Futhermore reoccurrence rates in late–life depression range from 50% to 90% in a period of 2 to 3 years. Thus the goal of treatment is not only acute recovery but also prevention of reoccurrence (Reynolds et al., 2006).

Most depression in older adults is managed in primary care settings (Pincus et al., 1998, Harman et al., 2003) but can be difficult to diagnose compared to mid-life depression. It is largely undetected and is often undertreated despite the availability of evidence based treatments. Primary care practitioners were found to detect only 40-50% of cases of late-life depression in a meta-analysis of 31 studies involving 52,513 individuals (Mitchell et al., 2010). Identification was lower in older adults than in younger adults. Recognition and treatment of depression in is particularly poor in long term care facilities. One study found that only half of patients in long term care facilities received antidepressants and of these one third received inadequate doses (Brown et al., 2002). This is particularly concerning given the higher rates of depression in these settings (Hoover et al., 2010).

1.2 Early life factors

Traditionally, aetiological models and preventative strategies aimed at reducing adult chronic diseases in adulthood have focused on the role of adult lifestyle factors such

as smoking, hypertension, obesity and cholesterol. However, it has become clear that the environment that an individual encounters earlier in life may be equally as important as experiences in adulthood in establishing risk of these diseases.

1.3.1 Developmental Origins of Health and Disease

In a series of ecological studies Barker and colleagues found strong geographic correlation between areas of England with the highest rates of mortality from CHD and stroke in the 1960s and 1970s, and areas with the highest rates of infant mortality in the early twentieth century (Barker and Osmond, 1986, Barker and Lackland, 2003). These areas also had high levels of short stature in the adult population (Barker and Lackland, 2003). The main causes of neonatal mortality in the early twentieth century were the health and physique of the mother, infant rearing practices and low birth weight (Woolf, 1947). In areas where mothers were well nourished neonatal deaths were low, even if living standards were poor (Barker et al., 1992a). On the other hand, post neonatal deaths were a result of overcrowding, large family size and high population density (Woolf, 1947) and were not associated with adult mortality independent of neonatal mortality (Barker et al., 1992a). Similarly short adult stature is a biological marker of poor growth in utero and poor living standards in childhood (Barker and Lackland, 2003). These geographic associations were not explained by differences in adult lifestyle behaviours (Gregory et al., 1990, Barker and Osmond, 1987). It was further found that people who were born in areas of high mortality, rather than people migrating to them, were at high risk of CHD and stroke, and this risk persisted even if they moved away from the area (Osmond et al., 1990).

These findings suggested that geographic variations in CHD and stroke mortality may originate through maternal influences associated with poverty, rather than through the effects of poor living standards in childhood or health behaviours in adulthood. Furthermore associations between birth weight and adult mortality suggested that low birth weight babies who survived infancy and childhood, might be at increased risk of CHD and stroke in later life.

These early findings led to two large studies of men born in the early twentieth century in Hertfordshire (n= 5654) and Sheffield (n=1586) with detailed birth records. Men with the lowest birthweights had the highest death rates from CHD and men with the highest birthweights had the lowest death rates from CHD (Barker et al., 1989). Mortality ratios also fell with increasing head circumference and increasing ponderal

index (Barker et al., 1993). This was found for those who were small at birth because of poor growth in utero rather than due to prematurity (Barker et al., 1993). These results were subsequently replicated in studies from other countries (Frankel et al., 1996, Stein et al., 1996), in women (Osmond et al., 1993, Rich-Edwards et al., 1997) and in more contemporary birth cohorts (Lawlor et al., 2005).

The importance of early life in the development of later disease was initially termed the Foetal Origins hypothesis or the Barker hypothesis. It proposed that coronary heart disease, stroke, and type 2 diabetes and the disorders related to them originate through responses to undernutrition during foetal life. These responses to environmental stimuli during critical or sensitive periods of development can trigger adaptions which can permanently alter the structure and physiology of the offspring in ways that lead to disease in later life (Barker, 1995, Barker, 2004). The Foetal Origins of Disease concept is an example of a predictive adaptive response (PAR). PARs are a form of developmental plasticity in which adaptive responses are made by the developing organism in response to its environment. These adaptions have no obvious immediate adaptive value but are made in expectation of the future environment (Gluckman and Hanson, 2004). A mismatch between the environment predicted prenatally and that encountered in later life may lead to disease. The greater the mismatch the higher the risk of disease.

It is now clear that growth during infancy and early childhood, in addition to foetal life, is linked to later disease and so the term Developmental Origins of Adult Health and Disease (Barker, 2004) has replaced the Foetal Origins hypothesis.

Birth weight has now been examined in relation to a wide range of health outcomes. An umbrella review of systematic reviews and meta-analyses published between 2005 and 2015 identified 39 articles including 78 associations which examined associations between birth weight and subsequent health outcomes (Belbasis et al., 2016). The most convincing evidence (defined as studies with >1000 cases and p values less than 1×10^{-6}) for associations between lower birth weight and increased disease risk in adulthood was found for all-cause mortality, cardiovascular mortality and coronary heart disease. Suggestive evidence (p value $<1 \times 10^{-3}$) was found for lower birth weight and asthma, chronic kidney disease and type 2 diabetes. Weak but still statistically significant evidence ($p<0.05$) was found for diastolic and systolic blood pressure, testicular cancer and metabolic syndrome. However 18 of the meta-analyses included in this umbrella systematic review highlighted that gestational age

was not considered as an adjustment variable in several observational studies which may have affected the results. This highlights the importance of including gestational age in studies assessing birth weight and later health.

Birthweight is not the only birth parameter related to later health and disease. In a series of studies conducted in Preston, UK, Barker and colleague found babies who had a small head circumference and who were thin at birth were more likely to develop high blood pressure (Barker et al., 1992b), impaired glucose tolerance and syndrome X- a combination of hypertension, non-insulin dependent diabetes and hyperlipidaemia in adulthood (Barker et al., 1993). Babies who were short at birth had higher rates of hypertension and raised plasma fibrinogen concentration in adulthood (Barker et al., 1992b). These findings have since been replicated in numerous other studies and relations between birth length and ponderal index, and disease in later life are well established (Risnes et al., 2011, Wang et al., 2014c).

1.3.1.1 Developmental Origins of Health and Disease: cSVD and depression

Although there are many studies indicating an association between size at birth and vascular risk factors in adulthood, there are few studies which have examined associations between size at birth and cSVD. Therefore it is unclear whether low birth weight increases risk of cSVD in later life. Studies have shown that mothers with a flat pelvis, have low-weight-for-gestational-age babies who later have an increased risk of stroke in adulthood (Heshmati et al., 2016, Osmond et al., 2007, Eriksson et al., 2000, Martyn et al., 1996). A flat pelvis is thought to affect placental growth and foetal development and indicate malnutrition in early childhood. Associations have been reported between birth weight and higher white matter integrity in the frontal lobes (Shenkin et al., 2009) and between higher ponderal index and higher total brain volume (Muller et al., 2014). On the other hand one study found no association between birth weight and WMHs (Muller et al., 2014).

Several studies and two meta-analyses have reported inverse associations between birth weight and depression in younger adults (Wojcik et al., 2012, Loret De Mola et al., 2014). However fewer studies have examined birth weight and late-life depression. One study found lower birth weight was associated with lifetime depression in a sample of Swedish women followed up until age 92 (Gudmundsson et al., 2011). However both Gale et al (2011) and Skogen et al (2013) found no

association between birth weight and depression at age 67-74 (Gale et al., 2011, Skogen et al., 2013).

1.3.1.2 Possible mechanisms

Two mechanistic hypotheses have been proposed to explain how foetal programing may occur: foetal malnutrition (Barker et al 1993) and foetal overexposure to glucocorticoids (Seckl, 2014). Evidence from animal and human studies supports both of these hypotheses and suggests they are not mutually exclusive. Maternal malnutrition or placental dysfunction can affect foetal glucocorticoid exposure (Chivers and Wyrwoll, 2017). Equally antenatal stress or maternal administration of glucocorticoids can affect feeding behaviour (Cottrell and Seckl, 2009).

Hales and Barker proposed that one of the main long term consequences of foetal undernutrition is the persistence of a foetal glucose- conserving adaption in response to intrauterine hypoglycaemia (Hales and Barker, 1992). When faced with energy insufficiency in utero, the foetus prioritises growth of vital organs such as the brain and heart, at the expense of other tissues such as muscle and the endocrine pancreas. This 'thrifty phenotype' may ensure survival of the foetus in the short term but can increase susceptibility to obesity, insulin resistance and type 2 diabetes when exposed to later environments with excess nutrition (Hales and Barker, 1992).

The role of nutrition in foetal programming is supported by epidemiological studies of foetal malnutrition during periods of famine. Those exposed to the Dutch Hunger Winter (1944-1945) have a higher risk of CHD, raised circulating lipids, raised concentrations of blood clotting factors, more obesity, glucose intolerance and type 2 diabetes, than aged matched non-exposed individuals (Ravelli et al., 1976, Ravelli et al., 1999, Roseboom et al., 2001, de Rooij et al., 2006b, de Rooij et al., 2007). Early exposure to the Chinese famine (1959-1961) was associated with increased BMI (Yang et al., 2008), hyperglycaemia (Li et al., 2010), hypertension (Huang et al., 2010) and metabolic syndrome (Li et al., 2011). In contrast, those who were exposed to the Leningrad Siege (1941-1944) show no difference in glucose intolerance, dyslipidaemia, hypertension or cerebrovascular disease in adulthood (Stanner et al., 1997). This may be because after the Leningrad Siege there were continuing food shortages in the U.S.S.R. This is in contrast to the Netherlands, where food supplies were returned to normal after the famine. This explanation would support the thrifty phenotype hypothesis.

Glucocorticoids play a vital role in normal foetal development and the maturation of tissues and organs (Cottrell and Seckl, 2009). However exposure to excess glucocorticoids during pregnancy correlates with reduced birth weight and adverse outcomes in the offspring. In animal models elevated cortisol during pregnancy is associated with low birth weight, glucose intolerance and increased blood pressure in the adult offspring (Moss et al., 2001, Lindsay et al., 1996, Nyirenda et al., 1998, Levitt et al., 1996). Evidence suggests that this also applies to humans. Studies of offspring of mothers with anxiety and depression have found reduced HPA axis function during childhood and adolescence (Murphy et al., 2015, Vedhara et al., 2012, O'Donnell et al., 2013). Babies who were small at birth had increased basal plasma cortisol as adults (Phillips et al., 2000). Furthermore exposure to exogenous synthetic glucocorticoids administered during pregnancy, and impairment of the placental barrier that protects the foetus from high levels of maternal glucocorticoids, is associated with small size at birth (French et al., 1999, Thorp et al., 2002, McTernan et al., 2001). These effects appear to be mediated at least in part via permanent changes in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis in the offspring (McGowan and Matthews, 2018).

Genome wide association studies (GWAS) have found associations between foetal (Horikoshi et al., 2016) and maternal (Beaumont et al., 2018) genotype and birth weight. Structural equation modelling (SEM) analysis found that maternal genotype acted on birth weight via the intrauterine environment rather than via effects on shared alleles with the foetus (Beaumont et al., 2018) . One GWAS study also found strong inverse genetic correlations between birth weight and systolic blood pressure and coronary artery disease (Horikoshi et al., 2016). Taken together these findings suggest that birth weight and its associations with adult health may have some genetic basis. This is supported by epigenetic studies which suggest that physiological changes induced by malnutrition or exposure to glucocorticoids are mediated in part by alterations in gene expression (Saffery and Novakovic, 2014).

1.3.2 Childhood factors

Factors in childhood have also been identified as important determinants of adult health. This next section will give an overview of the current literature examining associations between childhood cognitive ability, education and childhood SES and adult health. A detailed systematic review and meta-analysis of all published literature

examining childhood IQ, education childhood SES and risk of stroke, subclinical CVD and post-stroke depression is presented in Chapter 2.

1.3.2.1 Cognitive ability

The terms cognitive ability, intelligence and IQ are often used interchangeably in the cognitive epidemiology literature (Deary and Batty, 2007). Intelligence generally refers to psychometric intelligence measured using standard mental tests. These tests can measure specific abilities or can be used to determine general intelligence (often referred to as *g*), which is predictive of outcomes such as educational and occupational success (Jensen, 1998). IQ tests are used to describe a person's deviation from a population mean (usually standardised at a mean of 100 with SD of 15). In children, IQ is calculated by dividing their mental age by their chronological age multiplied by 100. Cognitive ability is likely to be a result of a combination of genetic and early life environmental factors (Gottfredson, 2004).

Data on childhood cognitive ability is a rare but valuable resource in aging research, allowing the assessment of cognitive functions that are unaffected by the process of aging and age related illness. In cases where it is not available, the National Adult Reading Test (NART) (Nelson and Willison, 1991), The Mill Hill and the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001) can be used to estimate premorbid IQ. These measures are built on the assumption that reading ability, an aspect of crystallised intelligence, remains constant regardless of age or damage to the brain (Bright et al., 2002) and scores in old age have been shown to correlate highly with childhood IQ even in early dementia (McGurn et al., 2004).

Childhood cognitive ability measured using standard tests in childhood or early adulthood, is an important early determinant of adult health. It is associated with general health (Martin et al., 2004) and longevity (Hart et al., 2003) and numerous chronic health outcomes including cardiovascular disease (Hart et al., 2004, Batty et al., 2005) and respiratory disease (Shipley et al., 2008). Several prospective cohort studies have found that higher childhood intelligence is associated with lower total mortality. A large cohort study of over 60,000 participants found that these associations were strongest for respiratory disease, CHD and stroke. Other notable associations were observed for deaths from injury, smoking related cancers, digestive disease and dementia (Calvin et al., 2017). A recent meta-analysis found that for

every standard deviation decrease in childhood cognitive ability, risk of cardiovascular events increased by 16% after adjustment for other risk factors (Dobson et al., 2017)

Childhood intelligence has been identified as an important factor in determining the effect of age-related changes in the brain. Higher childhood IQ is associated with cognitive reserve, correlates with cognitive ability in adulthood and may influence cognitive decline. Higher childhood cognitive ability is associated with decreased risk of stroke in some (Hart et al., 2004, Jokela et al., 2011, Lawlor et al., 2008), but not all studies (Batty et al., 2005, Hemmingsson et al., 2007) after adjustment for other risk factors. Furthermore poor performance on tests of crystallised intelligence has been associated with cognitive impairment following stroke (Makin et al., 2018, Sachdev et al., 2006).

Higher childhood IQ is associated with fewer WMH (Valdés Hernández et al., 2013a) and better white matter integrity in older adults (Deary et al., 2006, Shenkin et al., 2009). Shenkin and colleagues found that scores on cognitive tests at age 11 and scores on the NART correlated with diffusion tensor imaging parameters in the centrum semiovale at age 80 (Shenkin et al., 2003). A longitudinal study by Valdèz Hernàndez and colleagues reported an inverse relationship between age 11 IQ and WMH load around age 73. The strength of this relationship increased for those with evidence of previous clinical or subclinical stroke, with the volume of WMH almost doubled compared with those without stroke, independent of vascular risk factors (Valdés Hernández et al., 2013a) . A systematic review and meta-analysis of all published data on cognitive ability and risk of stroke and cSVD is presented in Chapter 2.

Interpretation of these studies may be difficult due to differing study designs, populations and measurements. Additional residual confounding by other factors that may affect childhood IQ and stroke must also be considered. These factors include genetics (Lee, 2003), early life social, environmental and nutritional factors (Dik et al., 2000, Lindmark et al., 2014), education (Lawlor et al., 2008) and SES (Jokela et al., 2011). It is important to consider all of these and how they relate to one another across the life course when considering risk of disease.

1.3.2.2 Education

Education is inversely associated with risk of dementia (Meng and D'Arcy, 2012), cognitive decline (Valenzuela and Sachdev, 2005) and stroke. Lawlor (Lawlor et al.,

2008) reported that for every additional category of education females were 41% and males 16% less likely to have a stroke. After adjustment for other early life factors such as IQ, this decreased slightly to 35% and 10% for females and males respectively. Furthermore longer educational history has been associated with events following stroke including lower frequency of cognitive deficits (Ojala-Oksala et al., 2012, Makin et al., 2018) and depression and improved long term survival after adjustment for age, stroke severity (Lindmark et al., 2014) and WMHs (Ojala-Oksala et al., 2012).

Several small studies have demonstrated the relationship between education and neuropathological changes associated with cerebrovascular disease (Del Ser et al., 1999). More education is associated with a thicker cortex (Cox et al., 2016) and higher cerebral (Foubert-Samier et al., 2012) and grey matter volume (Arenaza-Urquijo et al., 2013). People with lower levels of education have a higher frequency of cerebrovascular lesions and SVD (Farfel et al., 2013) including infarcts, lacunes, and white matter rarefaction (Del Ser et al., 1999). A systematic review and meta-analysis of all published data on education and risk of stroke and cSVD is presented in Chapter 2.

1.3.2.3 Childhood socioeconomic status (SES)

Health inequalities are well known and are outlined in publications such as the Marmot Report (Marmot, 2010). Poor socioeconomic conditions in early life make an important contribution to disease risk in adulthood including cardiovascular and cerebrovascular disease (Havranek et al., 2015). A systematic review of 40 studies investigating associations between childhood socioeconomic circumstances and ischaemic heart disease, stroke or combined CVD in adulthood, reported that the majority of studies show robust inverse association between childhood circumstances and CVD risk (Galobardes et al., 2006). This included 9 studies on childhood circumstances and risk of stroke, which provided the strongest evidence of an association. Childhood socioeconomic circumstance also predicts WMH burden in older adulthood (Murray et al., 2014). A systematic review and meta-analysis of all published data on childhood SES and risk of stroke and cSVD is presented in Chapter 2.

1.3.2.4 Education and childhood IQ and childhood SES

Educational attainment is strongly related to both cognitive ability and SES (Winkleby et al., 1992, Deary et al., 2007). Although education is often used as an indicator of SES, their relationship may be bidirectional, for example unfavourable socioeconomic circumstances can restrict opportunities for or access to higher education.

Several researchers have suggested that education may also be a surrogate for cognitive ability. Adjustment for education (Hemmingsson et al., 2007, Hart et al., 2004) and other socioeconomic factors (Hemmingsson et al., 2007, Lawlor et al., 2008) in the intelligence-health relation has largely shown a consistent and strong attenuating effect. Controlling for intelligence in the education-health (including stroke) relationship had little effect in one study (Link et al., 2008) but in another study, controlling for age 11 IQ reduced the association between education and cortical thickness by 23% at age 73 (Cox et al., 2016). Individuals with contrasting levels of education and IQ may provide a unique opportunity to separately assess these variables in relation to health. Link and colleagues (2008) reported that positive health outcomes were more strongly predicted by higher levels of education than higher levels of intelligence. This suggests that education may have a positive effect on improving health outcomes regardless of IQ. It is plausible that education may represent at least a partial proxy to childhood cognitive ability, as variance in educational outcome is to a substantial extent a reflection of differences in mental ability. However it can also be argued that education exerts at least a small amount of influence on health independent of the effect of childhood mental ability (Link et al., 2008) as indicated by the apparent protective effect of exposure to minimal amount of schooling on cerebrovascular disease risk (Farfel et al., 2013).

1.3 Summary

This chapter provides an introduction to the three key fields reported in this thesis; cerebrovascular disease particularly small vessel disease seen on neuroimaging, late-life depression and early life risk factors for adult disease.

This thesis will examine associations between early life factors and cerebrovascular disease and depressive symptoms in participants from 4 longitudinal cohort studies aged 60-82 years.

The aims of this thesis are to:

1. Systematically review and meta-analyse existing literature examining childhood cognitive ability, education and childhood socioeconomic status and risk of stroke, subclinical CVD and post-stroke depression.
2. Examine associations between structural brain changes detected on neuroimaging and self- reported symptoms of depression and anxiety.
3. Examine relationships between birth and childhood factors and structural brain changes detected on neuroimaging.
4. Examine relationships between birth and childhood factors and self-reported symptoms of depression and anxiety.

Early life factors which will be examined include birth parameters; exposure to famine during gestation, birth weight, birth length, ponderal index, head circumference and placental weight and childhood factors; childhood IQ, education (duration and attainment) and childhood SES. Cerebrovacular disease measures will include visual ratings of markers of cSVD and semi-automatic measures of WMH volume, whole and regional brain volumes and intracranial volume. A detailed description of these measures are given in Chapter 3.

A series of systematic reviews and meta-analyses of the current literature are presented in Chapter 2. Chapter 3 will provide background on the cohorts used in this Thesis. Chapters 4, 5 and 6 assess associations between cerebrovascular disease and depressive symptoms (Chapter 4) and associations between early life factors and cerebrovascular disease (Chapter 5) and depressive symptoms (Chapter 6). An overall summary of findings and discussion of methodological issues, implicactions of findings and suggestions for future research is presented in Chapter 7.

2. Systematic review and meta-analysis of early life factors for subclinical cerebrovascular disease, stroke and post-stroke depression.

This chapter contains data and figures published in

Backhouse, EV. McHutchison CA., Cvoro V., Shenkin SD., Wardlaw JM. Early life risk factors for cerebrovascular disease. A systematic review and meta-analysis.*Neurology*, 2017:88:976-984 (Section 3.1).

McHutchison, CA, Backhouse, EV. Cvoro V., Shenkin SD., Wardlaw JM. (2017) Education, socioeconomic status, and intelligence in childhood and stroke risk in later life. A meta-analysis. *Epidemio*l 2017; 28: 608-618 (Section 3.2)

Backhouse, EV. McHutchison CA., Cvoro V., Shenkin SD., Wardlaw JM. Education as a risk factor for post-stroke depression: A systematic review and meta-analysis. PLoS ONE (submitted)

2.1 Introduction

Cerebrovascular disease is common in older adults and can present as subclinical cerebral small vessel disease (cSVD) or clinical stroke. cSVD and stroke are a common cause of dementia and are associated with cognitive, psychiatric and physical disabilities (Wardlaw et al., 2013, Debette and Markus, 2010).

Depression is one of the most common neuropsychiatric disturbances following stroke, occurring in approximately 31% of patients during the first 5 years (Hackett and Pickles, 2014) People with post-stroke depression have worse functional outcomes, greater impairments and poorer recovery compared to non-depressed stroke patients (Robinson and Jorge, 2016).

Midlife vascular risk factors for cSVD such as hypertension, diabetes and several lifestyle factors are well established. However individual studies suggest that factors earlier in life including childhood cognitive ability (Valdés Hernández et al., 2013c, Jokela et al., 2011), education (Farfel et al., 2013, Lawlor et al., 2008) and socioeconomic status (Galobardes et al., 2006), may also contribute to CVD in later

life. The extent to which this applies across all studies and all three predictors (cognitive ability, education and SES) is not known.

Several risk factors for post-stroke depression have been proposed. These include gender, medical and psychiatric history, age and social support as well as factors relating to the stroke such as severity and degree of resulting disability (Robinson and Jorge, 2016, Jørgensen et al., 2016). However evidence supporting these factors is mixed and they only explain some of the variance in post-stroke depression. Few studies have examined the relationship between these childhood factors and post-stroke depression, but it is possible that an association exists via the relationship between early life factors and vascular disease. A previous review of 10 studies found no association between education and post-stroke depression (De Ryck et al., 2014). However, this review only included papers published in English between 1995 and 2012 which directly analysed education as a risk factor, and did not perform a meta-analysis.

To date, there are no known systematic reviews examining all evidence in relation to each of these early life factors, the risk of CVD and post-stroke depression. The current systematic review and meta-analysis of all published literature aimed to assess the relationship between:

1. Childhood or premorbid IQ, education, childhood SES and subclinical cSVD detected on neuroimaging or at post mortem.
2. Childhood or premorbid IQ, education, childhood SES and clinically evident stroke.
3. Childhood or premorbid IQ, education, childhood SES and diagnosis depression or depressive symptoms assessed after clinically evident stroke.

2.2. Methods

This review used the PRISMA and MOOSE guidelines (Stroup et al., 2000), and registered the protocol prospectively on Prospero (registration number: CRD42015016701).

2.2.1 Search methods

A detailed search strategy (Appendix 2.A) was developed and tested with help from an experienced librarian, to identify studies examining early life factors (education, childhood intelligence/premorbid IQ, childhood SES) and cerebrovascular disease including 'silent' (subclinical) features of cerebrovascular disease detected on neuroimaging or pathology; clinically overt cerebrovascular disease (i.e. stroke) and depression after stroke.

PsycINFO, MEDLINE and EMBASE were searched from inception for papers published until 30 November 2015 (cSVD and stroke) and 6th April 2016 (post-stroke depression) using OVID SP UI03.16.00.110. Reference lists of included papers and review articles were checked and the previous five years of *Stroke, Neurology* and *International Journal of Epidemiology* were hand searched.

Each abstract and title were screened by one reviewer and all potentially relevant full texts were screened independently by two researchers (EB or CM) for relevance. Disagreements regarding eligibility were resolved through discussion between the authors. Data from publications on the same cohort were taken from the most recent publication or the one with the largest sample. Eligible articles were grouped according to early life factor.

2.2.2 Inclusion criteria

Studies were included if they provided data on early life factors in relation to neuroimaging or pathology evidence of CVD, stroke or a diagnosis of depression or measurement of depressive symptoms following stroke in adulthood.

General intelligence (IQ) measurements performed up to age 18 and estimates of premorbid IQ using valid tools (e.g. Spot-The-Word Test) were included. Childhood SES measures such as parental occupation or parental education and all measures of childhood education were included (duration, attainment). Indictors of childhood SES included parental occupation, education and housing conditions.

‘Subclinical CVD’ was defined as white matter hyperintensities (WMH), lacunes, silent infarcts, or microbleeds according to the Standards for Reporting Vascular changes on nEuroimaging (STRIVE) (Wardlaw et al., 2013) criteria if on magnetic resonance imaging (MRI) or computed tomography (CT), or the equivalent features if on pathology. The method of quantification of WMH was noted, e.g. visual scale (Fazekas or other) or by volume. The Fazekas scale (Fazekas et al., 1987) rates WMH in the periventricular and subcortical region (0-3 scale). The Scheltens scale (Scheltens et al.) additionally scores hyperintensities in the basal ganglia and infratentorial region (0-24 scale). In both scales these regions can be reported separately or summed to give a total score. To allow direct comparison between studies correlation coefficients for IQ and periventricular WMH, deep WMH and deep WMH burden were meta-analysed.

‘Stroke’ was defined as a diagnosis based on clinical examination, neuroimaging, self-reported stroke or a diagnosis extracted from centralised health statistics (e.g. hospital and death registers etc.). Ischaemic stroke was the primary outcome and so haemorrhagic stroke or TIA only studies were excluded. Studies examining a combination of ischaemic, haemorrhagic stroke and TIA as these samples consisted predominantly of ischaemic stroke patients were included.

Depressive symptoms were defined as any measurement of mood using a valid tool that was conducted at any time following a stroke. These included diagnostic tools such as The Diagnostic and Statistical Manual of Mental Disorders (DSM) and scales such as the Beck’s Depression Inventory, the Montgomery Asberg Depression Rating Scale (MADRAS) and the Hamilton Depression Rating Scale (HDRS) (higher score indicates worse depression/depressive symptoms). All measures of childhood education were included (duration, attainment).

Papers with less than 50 patients, those focusing on a particular patient population (e.g. Parkinson’s disease), without primary data, published only in abstract, or not reporting data on humans aged 18 or over were excluded. Papers in any language were considered.

2.2.3 Data extraction and quality assessment

One reviewer (EB or CM) extracted data and cross-checked each extraction form; JMW, SDS, VC cross-checked a sample. Data were extracted data onto an electronic spreadsheet. This included study and participant characteristics, including total

number of participants by early life factor, definition and measurement of early life factor, outcome and statistical results, including whether the effect size was adjusted for vascular or other risk factors, or crude.

Methodological quality of each study was assessed for six potential sources of bias:(Hayden et al. 2006) representativeness of the sample to the population, study attrition reported, how early life factor and outcome were measured, adjustment for confounders and appropriateness of the statistical analysis. Each item was assigned a score of 1-4 (corresponding to unclear, no, partly, yes), giving a total score of 24, higher scores indicating better quality.

2.2.4 Statistical analysis

Within each early life factor, papers were grouped according to the outcome statistic (e.g. Odds Ratio (OR), mean values). Where multiple statistics were reported, the one that maximised data available for meta-analysis was used. Markers of CVD were analysed together to produce an overall result, and separately in prespecified subgroup analysis.

Lowest and highest IQ were compared in instances where no overall HR was reported. Two studies (Vemuri et al., 2015, Sampson et al., 2003) reported median scores as a measure of central tendency. Due to the small amount of available data, these medians were used in the meta-analysis.

Definition of education was based on the categorisation of education in the majority of papers within each outcome (cSVD, stroke and depression). With the exception of one study (Farfel et al., 2013), papers examining cSVD defined low education as approximately 6-8 years and high education as 9 years and above. This corresponded to less than a high school education and high school and above in those papers reporting education in terms of attainment. In papers examining stroke low education was defined as approximately 8-10 years of full time education or less and high education as 11 years and above. In papers examining depression low education was defined as approximately 6-8 years (or less than high school) and high education as 9 years and above (or high school and above).

Most papers reporting childhood SES used father's or head of household's occupation, generally classed as manual or non-manual to indicate low and high SES.

Other indicators used were parental education level and financial troubles in childhood.

All results were standardised to represent a reference level of high IQ, education and SES. Review Manager V.5.3 was used to calculate overall ORs, RRs and mean differences (MD) and 95% confidence intervals. Correlation coefficients were analysed using the package 'metacor' for R V.3.0.1. Where possible, risk factor adjusted results were used from studies. Where necessary, odds ratios were calculated from frequency data. Papers which reported means or medians were analysed separately. Medians were included in the mean difference analysis as medians. A random effects model was used in anticipation of between study heterogeneity and assessed heterogeneity using the I^2 statistic. Funnel plots and Egger's test were used to assess publication bias.

For papers examining risk of stroke sensitivity analyses were pre-specified to examine the effect of adjusted versus unadjusted results, participant age, sampling method and outcome measurement. Several post hoc sensitivity analyses were performed on papers examining post-stroke depression.

2.3 Results

The search identified 19,180 titles and abstracts for screening after removal of duplicates from which 1,217 full text articles were identified (Figure 2.1). Of these 905 were excluded. The most common reason for exclusion was lack of an appropriate outcome. This left 153 papers which were included in the meta-analysis: 30 papers examined cSVD; 90 papers examined stroke and 33 papers examined post-stroke depression (figure 2.1).

Results will now be presented by early life factor (childhood IQ, education and childhood SES) for each outcome (cSVD, stroke and post-stroke depression). Due to the large number of studies identified, author names are not referenced directly in sections which include results from more than 10 studies. Author names can be found in the appropriate figures and full details of all studies are given in Appendix 2B-D.

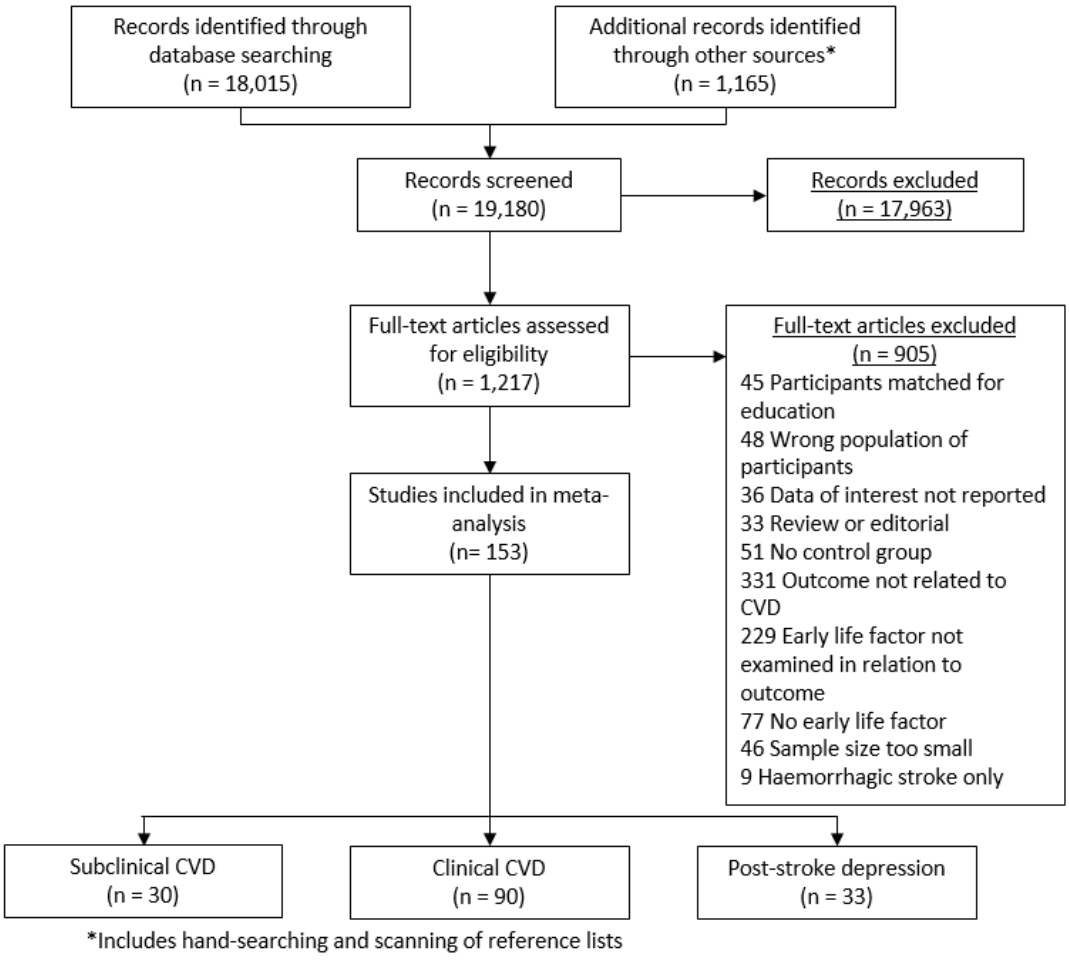


Figure 2.1: PRISM flow chart of search and study selection

2.3.1 Early life factors and risk of cSVD

Thirty papers which examined early life factors and subclinical CVD met inclusion criteria. Most studies assessed CVD with neuroimaging; two population studies assessed CVD at post mortem (Brayne et al., 2010, Farfel et al., 2013). These studies are summarised in Table 2.1. Full details of all included studies are provided in Appendix 2B.

Table 2.1: Summary of studies included in systematic review of early life factors and subclinical CVD

	Childhood IQ	**Education**	**Childhood SES**
Number of papers identified	8	30	1
Number of studies included	5	26	1
Study setting			
Population	4	16	1
Hospital	0	1	0
Community	1	6	0
Outpatient clinic	0	5	0
Autopsy	0	1	0
Total number of participants	1,512	22,013	243
Age range of included studies	60-78.3	45-85.2	68
Outcome			
WMH	5	16	1
Micro-bleeds	0	4	0
Lacunes	0	2	0
Infarcts	0	4	0
SVD	0	6	0
Quality score[a]	21 (1)	21 (2)	21
Range	17-22	17-24	21

Some studies fall into multiple categories; [a] Median (interquartile range)

SES: socioeconomic status; WMH: white matter hyperintensities

Quality assessment and publication bias

Quality scores ranged from 17-24/24. Most papers scored 'good' (3/4) on statistical analysis and measurement of early life factor but less well on confounding factors and sample representativeness (Figure 2.2). The scale did not weight different items of the scale.

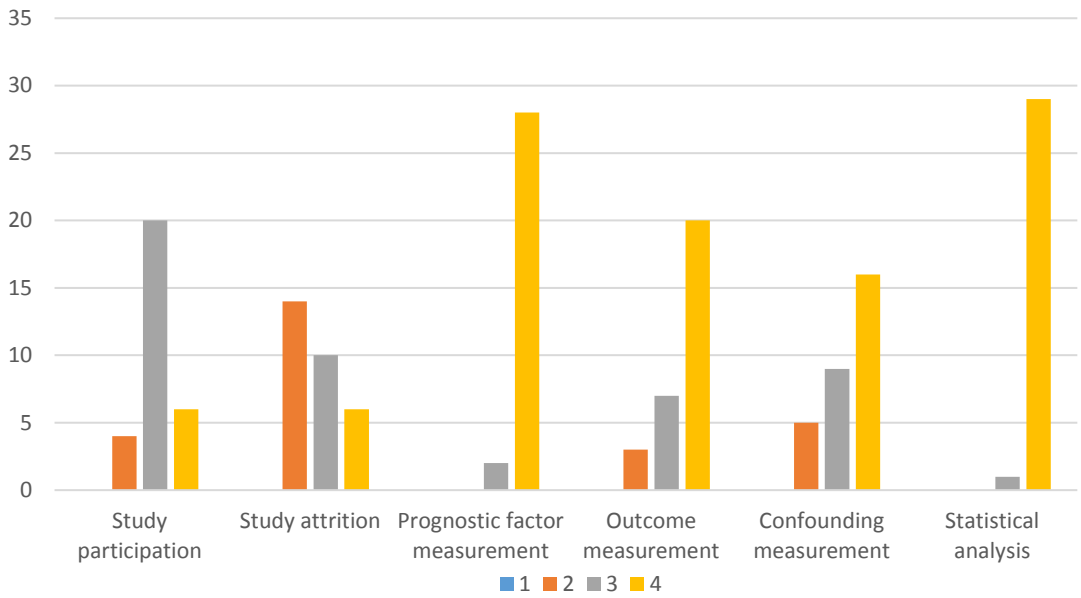
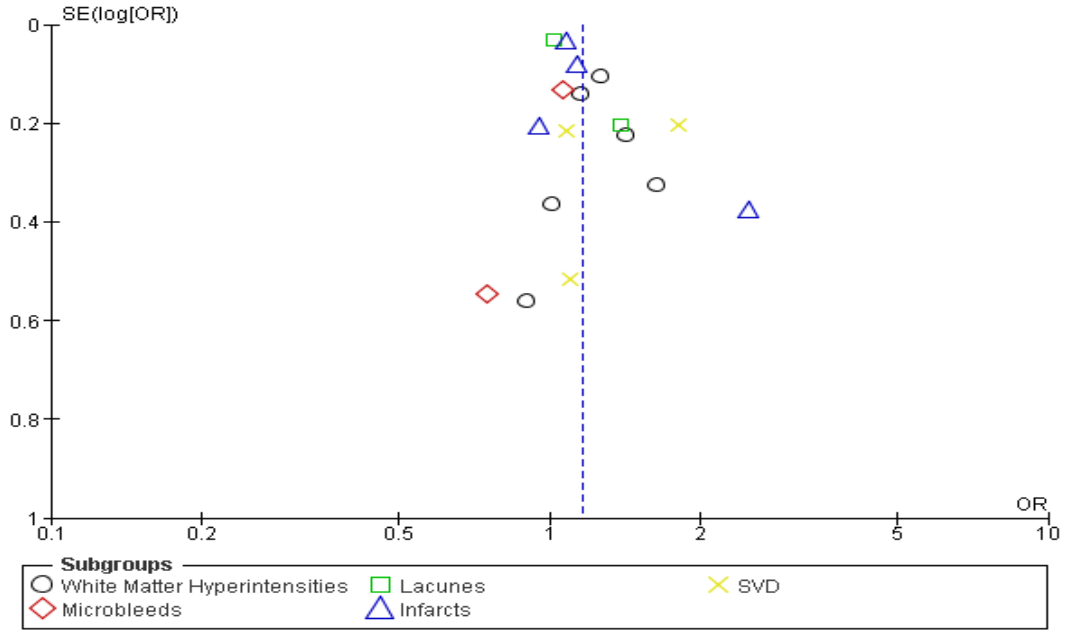


Figure 2.2: Quality assessment for studies examining early life factors and cSVD: Frequencies of scores on individual quality items.

It was not possible to determine publication bias for all analyses due to the small number of studies in some comparisons. However Egger's regression test showed evidence of publication bias in some studies (p<0.001) (Figure 2.3).



Egger's regression: t= 25.29, p<0.001

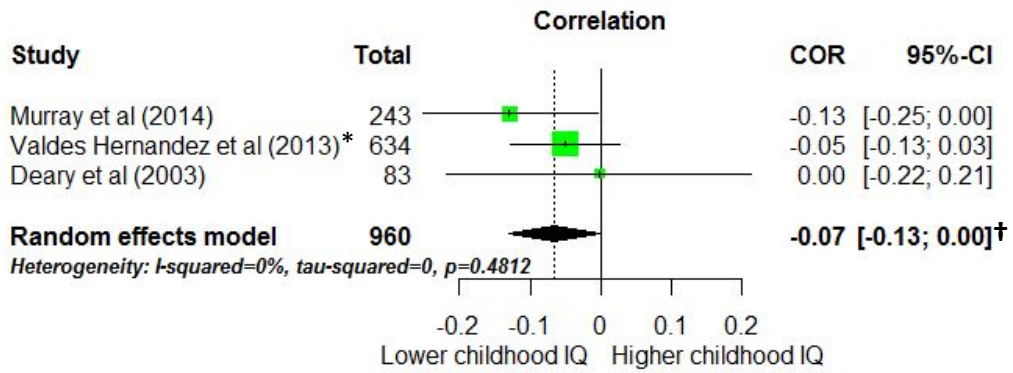
Figure 2.3: Publication bias of studies examining early life factors and cSVD.

2.3.1.1 Childhood IQ

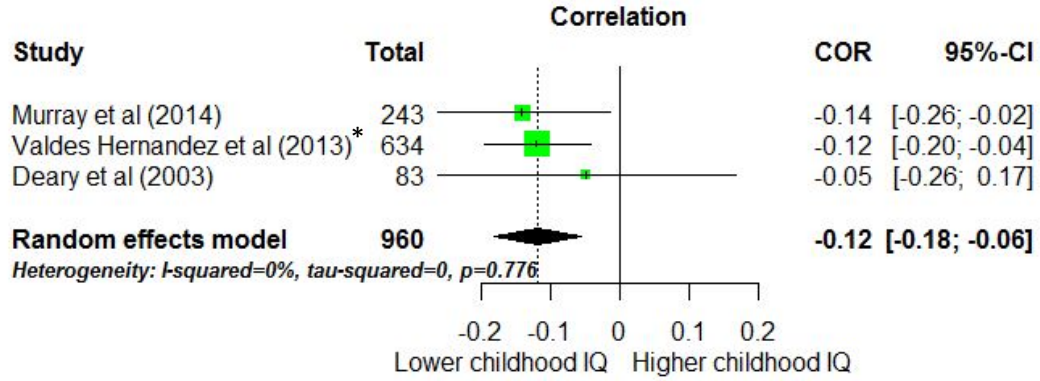
Five studies (Christensen et al., 2007, Deary et al., 2003, Murray et al., 2014, Salarirad et al., 2011, Valdés Hernández et al., 2013c) reported in eight papers, examined the relationship between childhood IQ and subclinical CVD. These included 1,512 participants aged 60 to 78 years old at the time of MRI. All studies assessed WMH as the only marker of CVD on MRI measured using the Fazekas or Scheltens scale, and reported results as correlations. Most studies used IQ obtained at age 11 (four papers (Deary et al., 2003, Murray et al., 2014, Salarirad et al., 2011, Valdés Hernández et al., 2013c) while one (Christensen et al., 2007) estimated premorbid IQ in adulthood using the Spot-the-Word test.

Overall, lower childhood IQ was associated with increased deep WMH scores (r= -0.066, 95% CI -0.129 to -0.003, p=0.04 Figure 2.4A), periventricular WMH scores (r=-0.12, 95% CI -0.182 to -0.056, p= <0.001, Figure 2.4B) and total WMH scores (*r*= -0.07, 95% CI = -0.12 to -0.02, p=0.007, Figure 2.4C). One study (Valdés Hernández et al., 2013c) provided risk factor-adjusted results. Heterogeneity between studies was low (I^2 0% p=0.66).

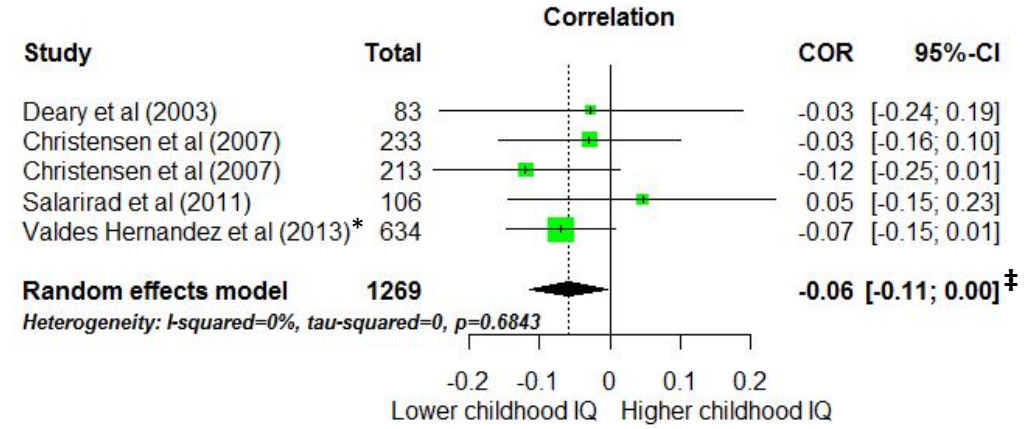
A



B



C



Footnotes: * Adjusted for age, sex and hypertension; † Before rounding 95% CI= -0.129 to -0.003; ‡ Before rounding 95% CI= -0.113 to -0.004

Figure 2.4 (A-C) Forest plots showing correlation between (A) childhood IQ and deep white matter hyperintensity burden, (B) periventricular hyperintensity burden and (C)

total white matter hyperintensity burden: Lower childhood IQ was associated with higher WMH burden in late life.

2.3.1.2 Education

26 studies reported in 30 publications examined education and subclinical CVD, including 22,357 participants aged 45-84 at the time of the MRI. The most common individual markers of subclinical CVD were WMH (sixteen studies), micro-bleeds (four studies (Miwa et al., 2014, Qiu et al., 2010, van Norden et al., 2011, Wiegman et al., 2014)), infarcts (four studies (Brayne et al., 2010, Elkins et al., 2006, Mortamais et al., 2014, Tsukishima et al., 2001)) and lacunes (two studies (Farfel et al., 2013, Brayne et al., 2010) and six studies (Farfel et al., 2013, Jokinen et al., 2009, Minn et al., 2013, Sims et al., 2014, Tsukishima et al., 2001, Vemuri et al., 2015) examined combined markers of cSVD.

Education level was assessed as duration (i.e. <8years vs ≥8years) in 7 studies (Brayne et al., 2010, Christensen et al., 2009, DeCarli et al., 2008, Minn et al., 2013, Mortamais et al., 2014, Schretlen et al., 2007, Tsukishima et al., 2001) and attainment (i.e. primary vs secondary school) in 12 studies. 7 studies (Boone et al., 1992, Dufouil et al., 2003, Jokinen et al., 2009, Miwa et al., 2014, Wiegman et al., 2014, Yamawaki et al., 2015, Vemuri et al., 2015) reported mean years of education.

Education level and subclinical CVD

Of the 26 studies, 16 reported education level (either duration or attainment) for individuals with subclinical CVD (WMH, micro-bleeds, lacunes, infarcts and SVD) (Figure 2.5). One study (Tsukishima et al., 2001) examined two different groups of participants and two different markers of cSVD and so is included in figure 2.5 twice.

Three studies (Brayne et al., 2010, Farfel et al., 2013, Mortamais et al., 2014) reported education data in relation to more than one marker of CVD. To avoid double counting, participant data from only one CVD marker could be included when calculating the odds ratio for all participants. Infarct data was excluded from the first study (Brayne et al., 2010) as it was unclear whether the infarcts were silent. Lacune data from the second (Farfel et al., 2013) was captured in SVD score and was therefore excluded. The third study (Mortamais et al., 2014) had infarct and WMH data. Sensitivity analysis showed that exclusion of infarct data from this study resulted in an overall

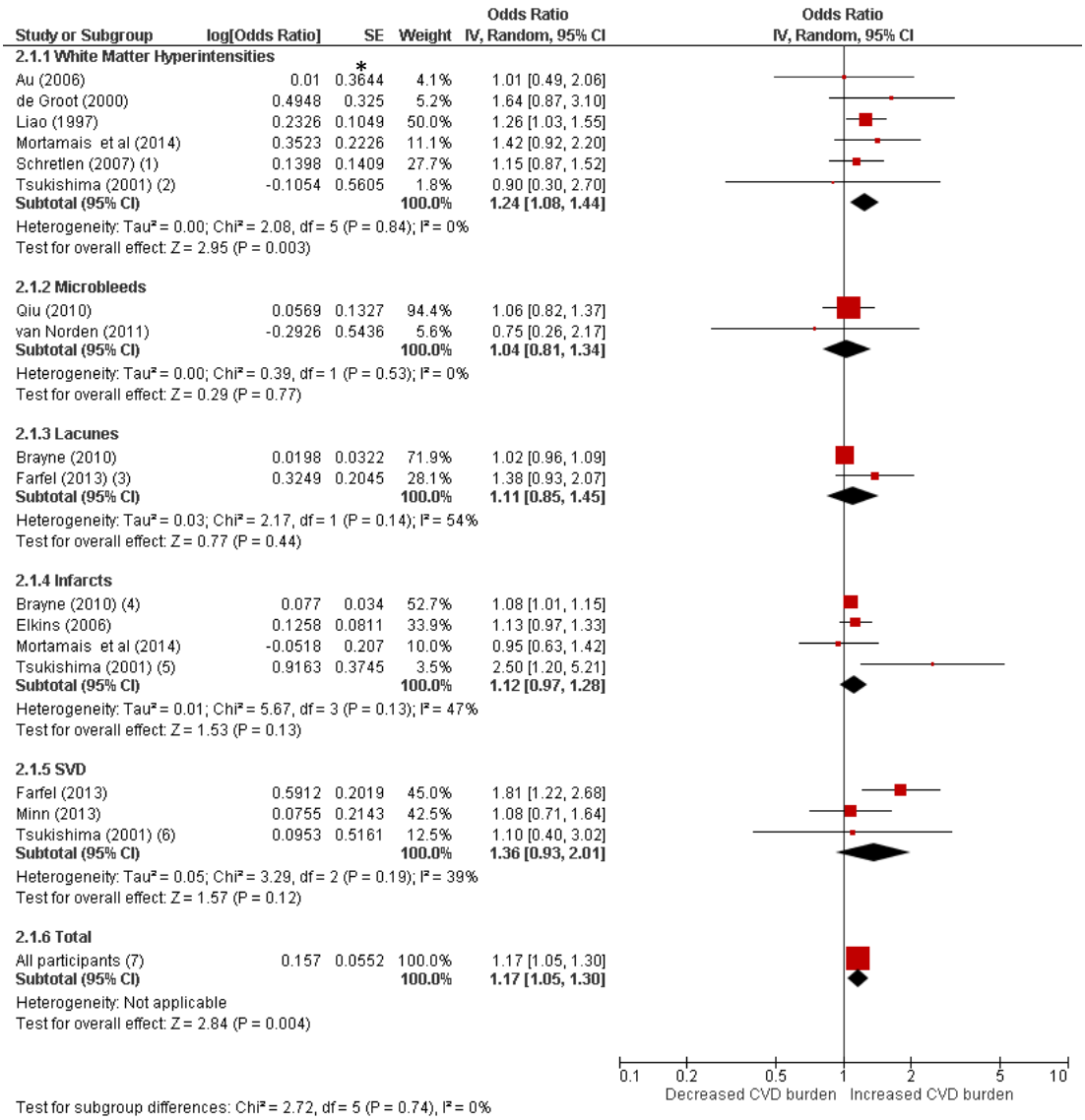
odds ratio of 1.17, (95% CI 1.05 to 1.31, P=0.003, figure 2.3). Exclusion of WMH data reduced the overall odds ratio to 1.14 (95% CI 1.03-1.27, p=0.01).

Further sensitivity analysis excluding two papers with unclear definitions of CVD markers (Brayne et al., 2010, Elkins et al., 2006) and two with the lowest quality score (Brayne et al., 2010, Farfel et al., 2013) did not materially alter results (OR 1.20 95% CI 1.05 to 1.36, p=0.007; OR 1.20 95% CI 1.07 to 1.35, p=0.002 respectively).

The definition of low education varied especially in studies of infarcts (e.g. less than high school (Elkins et al., 2006), six (Tsukishima et al., 2001), seven (Brayne et al., 2010), and eight years (Mortamais et al., 2014) of education) and SVD (less than one year (Farfel et al., 2013), six years (Tsukishima et al., 2001) and seven years (Minn et al., 2013) of education).

Subgroup analysis for individual CVD features (figure 2.5), which included all 16 studies, showed lower educational level was associated with more WMH (six (Au et al., 2006, de Groot et al., 2000, Liao et al., 1997, Mortamais et al., 2014, Schretlen et al., 2007, Tsukishima et al., 2001) studies n=5,564, OR 1.24, 95% CI 1.05 to 1.47, p=0.01) but no difference in infarcts (four studies, (Brayne et al., 2010, Elkins et al., 2006, Mortamais et al., 2014, Tsukishima et al., 2001) n=5,184, OR 1.04, 95% CI 0.81 to 1.34), micro-bleeds (two studies, (Qiu et al., 2010, van Norden et al., 2011) n=3,618, OR 1.04, 95% CI 0.81 to 1.34) or lacunes (two studies, (Brayne et al., 2010, Farfel et al., 2013) n= 1,465, OR 1.11, 94% CI 0.85 to 1.45). Low education was also not associated with cSVD which included multiple markers of CVD (three studies (Farfel et al., 2013, Minn et al., 2013, Tsukishima et al., 2001)) n=1,333, OR 1.36, 95% CI 0.93 to 2.01).

Four studies (Annweiler et al., 2014, DeCarli et al., 2008, Murray et al., 2014, Sims et al., 2014) (n=949) could not be included in the meta-analysis due to the statistics reported. Two reported a significant correlation between education and deep WMH (r=-0.149, p<0.05), PVH (Murray et al., 2014) (r=-0.167, p<.05, n=243) and subclinical CVD (Sims et al., 2014) (β= -0.258, p=0.01, n=172) and two reported non-significant associations between education and overall WMH (β=0.43, p=0.238, n=133), periventricular WMH (β=0.08, p=0.598, n-=133), deep WMH (Annweiler et al., 2014) (β= -0.01 p=0.964, n=133) and log transformed WMH (DeCarli et al., 2008) (F=0.10, p=0.74, n=401).



NOTE: Results are unadjusted unless stated otherwise

Figure 2.5: Forest plot comparing low education vs high education and risk of subclinical CVD features (OR< 1= low education decreases risk of having features; OR >1= low education (<9 years) increases risk of having CVD features)

Mean years of education in those with and without CVD markers

Seven studies (Boone et al., 1992, Dufouil et al., 2003, Jokinen et al., 2006, Miwa et al., 2014, Vemuri et al., 2015, Wiegman et al., 2014, Yamawaki et al., 2015) (n=3,016) reported mean years of education by presence/absence of several CVD markers (Figure 2.6). Overall, mean difference in years of education did not differ between those with subclinical CVD and those without, either overall (seven studies, n=3,016, MD= -0.07 years 95% CI -0.19 to 0.34, p=0.59), or when analysis was restricted to individual CVD markers.

Heterogeneity between studies was low (I^2 5%, p=0.13).

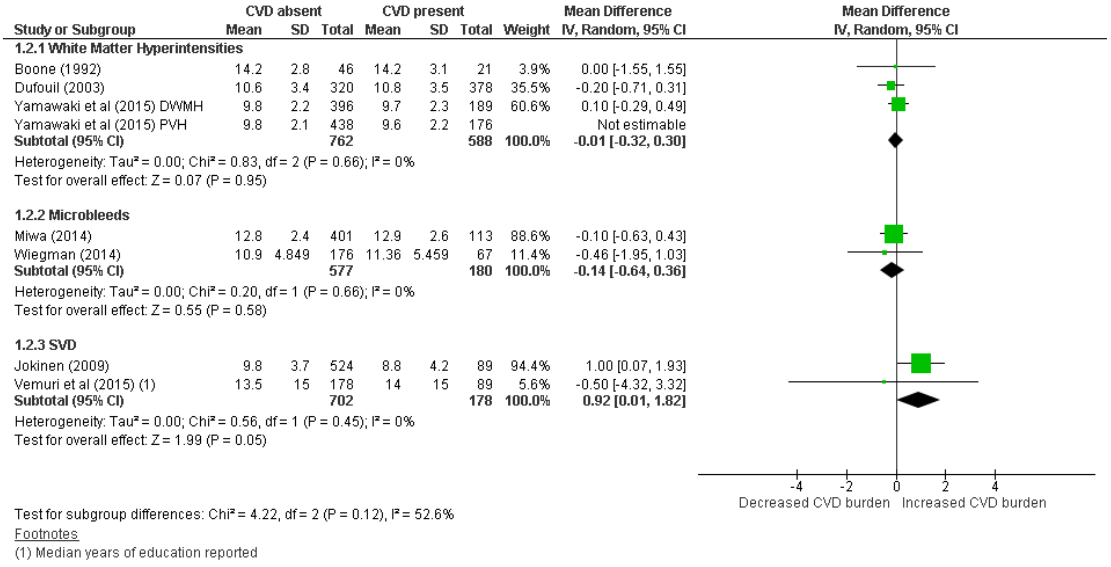
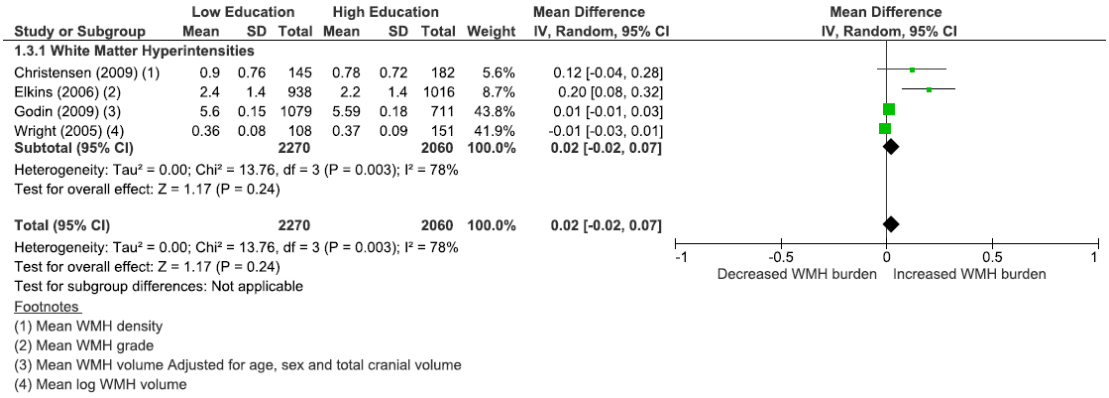


Figure 2.6: Mean years of education for those with lower vs higher CVD burden, random effects model for the mean difference (negative mean difference = low education decreases WMH volume; positive difference = low education increases WMH volume)

Mean volume of WMH in those with low and high education

There was no difference in mean WMH volume between those with high and low levels of education (four studies (Christensen et al., 2009, Elkins et al., 2006, Godin et al., 2009, Wright et al., 2005) n=4,330 MD= 0.02, 95% CI -0.02 to 0.07, p=0.24 random effects, Figure 2.7). However, there was substantial heterogeneity between studies (I^2 78% p=0.003) but the small number of studies (four) precluded producing a funnel plot to assess publication bias.



NOTE: Results are unadjusted unless stated otherwise

Figure 2.7: Mean WMH volume in those with low versus high levels of education, random effects model for the mean difference (negative mean difference = low education (<high school) decreases WMH volume; positive difference = low education (<high school) increases WMH volume)

2.3.1.3 Childhood socioeconomic status

One study (Murray et al., 2014) (n=243) found that lower father's occupation (measured as manual vs office-based in six categories with a lower score indicating manual occupation and more childhood deprivation) correlated with more deep WMH (r=-0.181, p<0.05) and periventricular WMH (r=-0.146, p=<0.001) at age 68.

2.3.2 Early life risk factors for stroke

Ninety papers examined early life factors and risk of stroke (Figure 2.1; see Table 2.2 for summary and Appendix 2C for full details of included papers). Although most Continents were represented by one or more studies, most studies took place in North America or Europe.

Table 2.2: Summary of studies included in systematic review of early life factors and risk of stroke

	Education	**Childhood SES**	**Childhood IQ**
Number of studies identified	108	15	13
Number of studies included	79	10	9
Study setting			
Population	48	8	6
Hospital	22	1	3
Community	5	1	0
Outpatient clinic	9	0	0
Total number of stroke patients	141,788 [a]	13,210 [a]	9,685
Total number of non-stroke patients	2,572,839 [b]	1,318,962 [a]	1,200,264
Age range of included studies	18-88	30-80	36-77
Quality Score [c]	22 (2)	22 (1.5)	22 (2.5)

Some studies fall into multiple categories.

[a] Data not reported for 1 study.

[b] Data not reported for 3 studies.

[c] Median (Interquartile range).

SES: socioeconomic status.

Quality assessment and publication bias

The quality of the included papers was good, with scores from 18-24/24 (median=22). Sample representativeness was the lowest scoring subscale, with statistical analysis being the highest scoring (figure 2.8).

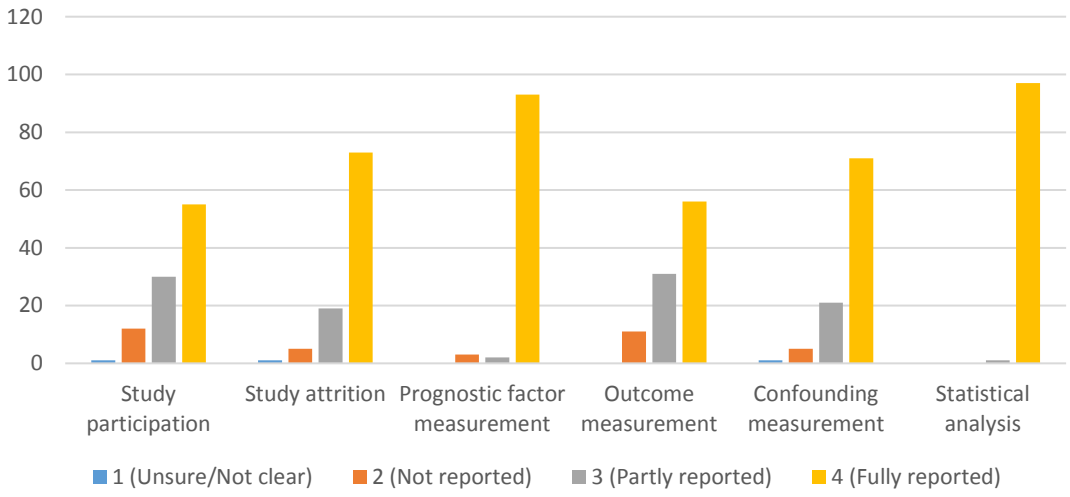
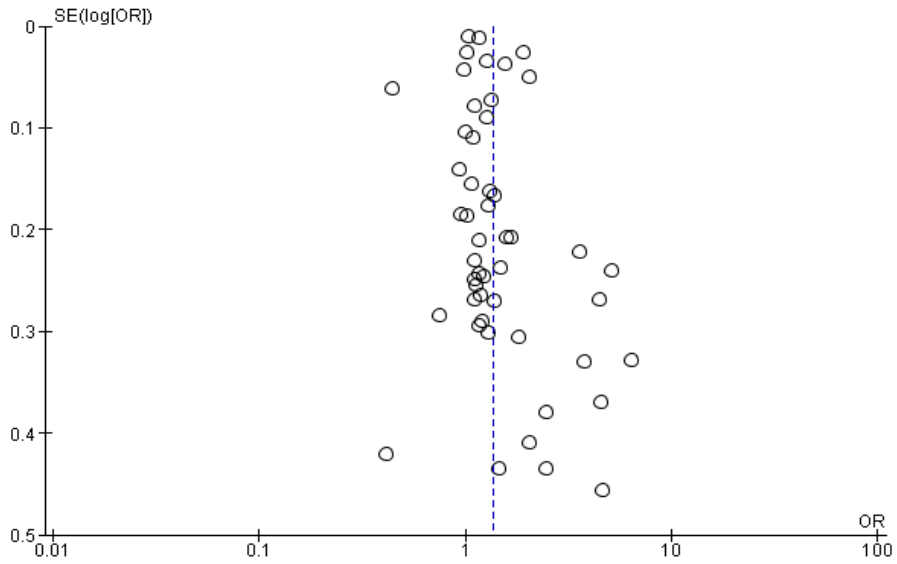


Figure 2.8: Quality assessment for studies examining early life factors and stroke: Frequencies of scores on individual quality items

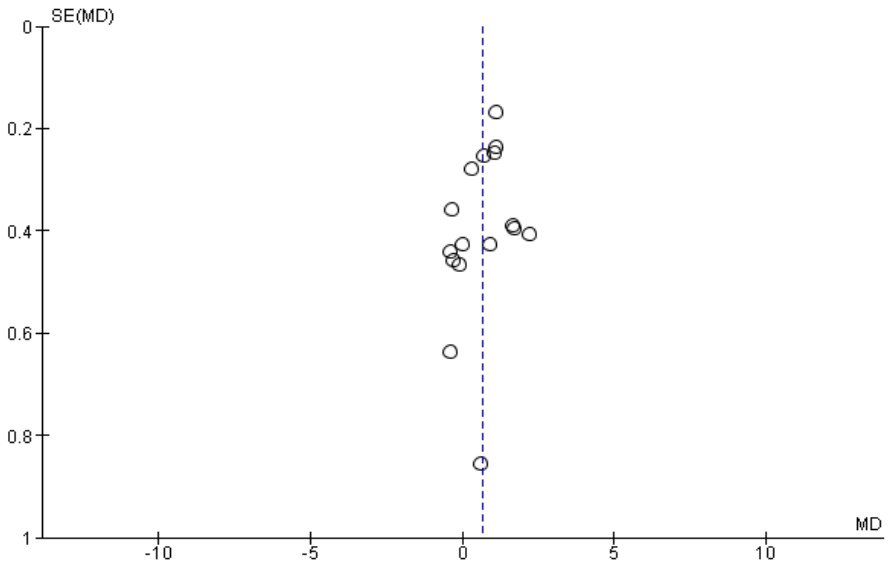
Egger's regression test showed evidence of publication bias in some studies ($p<0.05$) (see Figures 2.9 A-C).

A



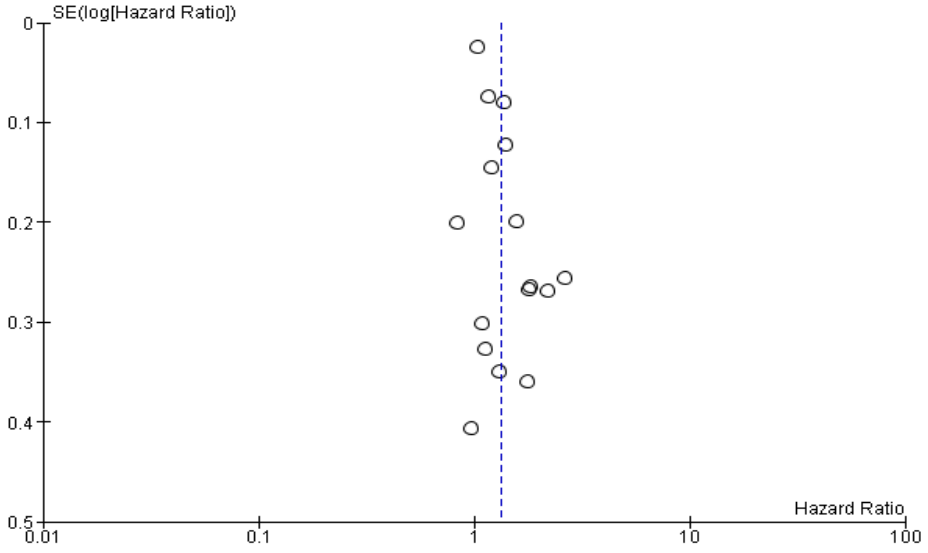
Egger's regression: t= 19.21, p<0.001

B.



Egger's regression: t= 3.15, p=0.01

C.



Egger's regression: t= 18.02, p<0.001

Figure 2.9 (A-C): Funnel Plots for analysis of publication in studies reporting (A) odds ratios (B) mean differences (C) hazard ratios for education and risk of stroke.

2.3.2.1 Childhood IQ

Nine studies, (Wennerstad et al., 2010, Hemmingsson et al., 2007, Jokela et al., 2011, Lawlor et al., 2008, Kessels et al., 2006, Batty et al., 2005, Brodaty et al., 2010, Kajantie et al., 2012, Sampson et al., 2003) reported in 13 papers (total n=1,209,952), examined childhood/premorbid IQ and stroke. Five studies (Batty et al., 2005, Hemmingsson et al., 2007, Lawlor et al., 2008, Wennerstad et al., 2010, Kajantie et al., 2012) adjusted for confounders, of which three adjusted for vascular risk factors (Wennerstad et al., 2010, Hemmingsson et al., 2007, Kajantie et al., 2012).

Six papers measured IQ in childhood/early adulthood (Wennerstad et al., 2010, Hemmingsson et al., 2007, Jokela et al., 2011, Lawlor et al., 2008, Batty et al., 2005, Kajantie et al., 2012) and three estimated premorbid IQ in adulthood using the NART (Kessels et al., 2006, Brodaty et al., 2010, Sampson et al., 2003) resulting in 9,685 strokes and 1,200,267 stroke-free participants aged 36-77 years old at the time of follow-up or stroke.

Five studies were meta-analysed (Wennerstad et al., 2010, Hemmingsson et al., 2007, Lawlor et al., 2008, Batty et al., 2005, Kajantie et al., 2012) (9,087 strokes, 1,191,612 stroke-free participants) reporting HRs and three (Kessels et al., 2006, Brodaty et al., 2010, Sampson et al., 2003) (322 strokes, 308 stroke-free participants) reporting the average IQ score and risk of stroke. In subjects with a lower versus higher childhood IQ, stroke risk was increased (HR=1.17, 95% CI=1.00 to 1.37, p=0.04, I^2 55%; MD=5.52, 95% CI=0.11 to 10.94, p=0.05, I^2 72%; figures 2.10A and 2.10B).

The remaining study (Jokela et al., 2011) reported an OR which could not be included in the meta-analyses. Consistent with the other studies, it demonstrated that higher IQ was associated with decreased stroke risk (OR=0.85, 95% CI=0.74 to 0.99, p<0.05) after adjusting for demographic and SES factors. Removal of one large study (Lawlor et al., 2008) reduced heterogeneity to zero (overall HR=1.09, 95% CI=1.08 to 1.10, p<0.001).

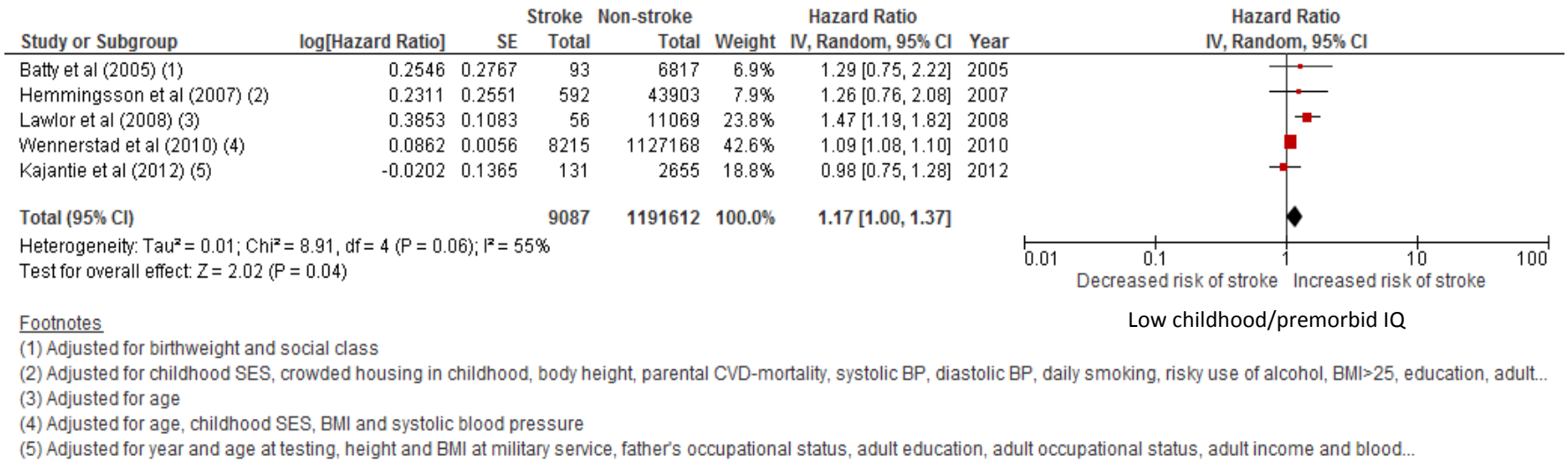


Figure 2.10A: Childhood/premorbid IQ (low versus high) and risk of stroke, hazard ratio, random effects model (Hazard Ratio<1 indicates low IQ decreases risk of stroke; >1 = low IQ increases risk of stroke

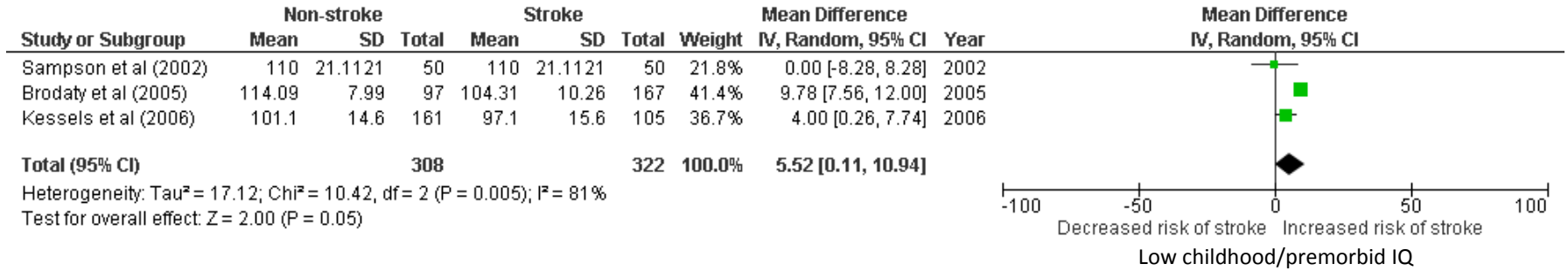


Figure 2.10B: Childhood/premorbid IQ by mean IQ score in persons with and without stroke, random effects model for the mean difference (negative mean difference :lower IQ decreases risk of stroke and positive mean difference:lower IQ increases risk of stroke).

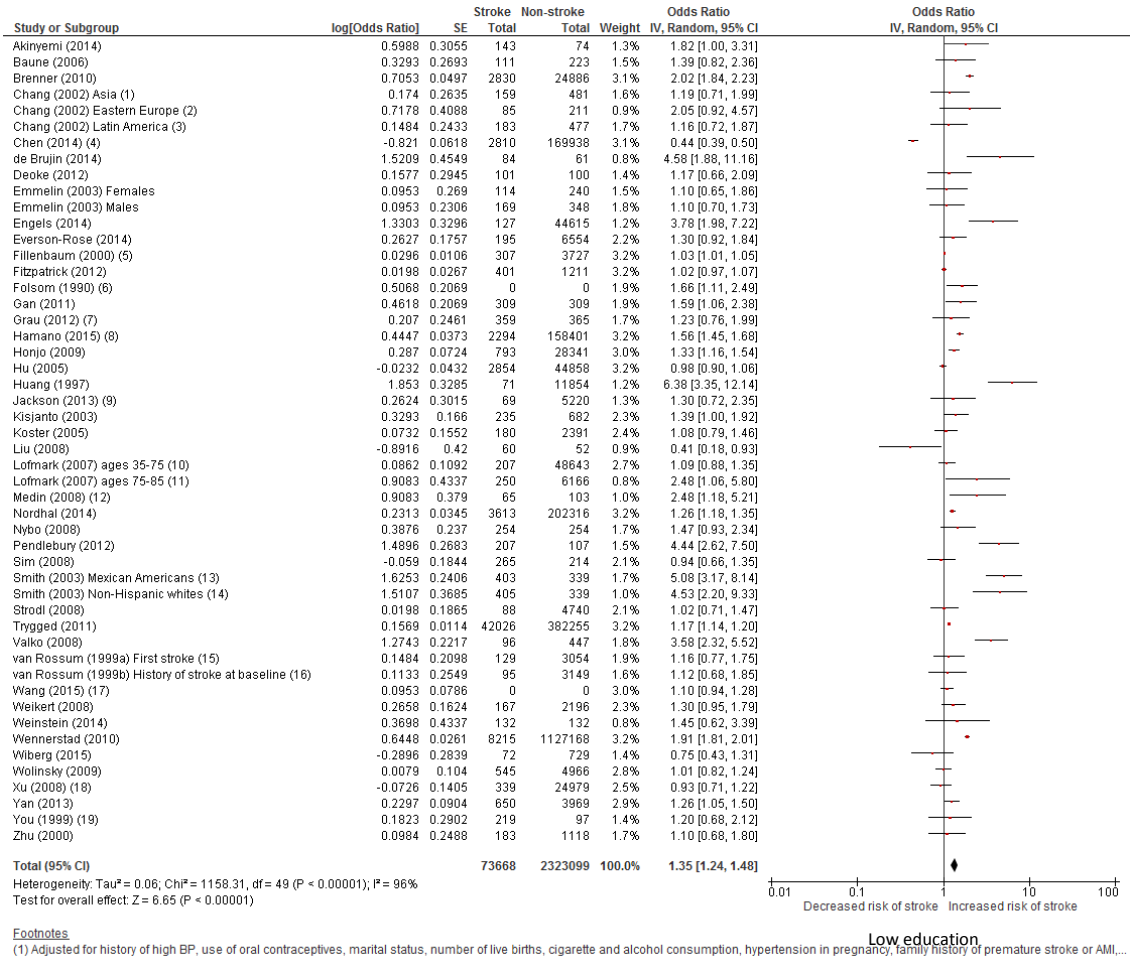
2.3.2.2 Education

Seventy nine studies, reported in 108 papers (total n=3,602,148), examined education and risk of stroke. Thirty-one papers reported adjusted results, of which 16 adjusted for vascular risk factors.

Twenty-five papers reported frequencies of stroke by duration of education. These frequencies were used to calculate unadjusted ORs which were analysed with 19 other papers that reported ORs (total 73,668 strokes and 2,323,099 stroke-free participants). Mean years of education was reported in 16 papers (3,209 strokes and 19,712 stroke-free participants), 13 reported HRs (4,320 strokes and over 163,096 stroke-free participants) and five reported RRs (Andersen et al., 2014, Gillum and Mussolino, 2003, Lindenstrøm et al., 1993, Lisabeth et al., 2007, Hart et al., 2000) (56,593 strokes and over 18,061 stroke-free participants (note that in all analyses the true denominator is larger than the number shown because not all studies reported the number of stroke-free participants)).

Overall, less versus more education was associated with an increased risk of stroke (OR=1.35, 95% CI=1.24 to 1.48, p<0.001, I^2=96%; MD=0.66, 95% CI=0.31 to 1.01, p<0.001, I^2=77%; HR=1.33, 95% CI=1.71 to 1.53, p<0.001, I^2=70%; RR=1.39, 95% CI=1.08 to 1.78, p=0.009, I^2=90%; figures 2.11A-D). There was between-study heterogeneity for all comparisons, ranging from 76% to 96%. One paper(de Jesús Llibre et al., 2010) reported a stroke prevalence ratio for those with higher education (PR=0·9, 95% CI=0·6 to 1·1; 229 strokes and 2,786 stroke-free participants) so could not be included in the meta-analysis.

In sensitivity analyses, examined education and stroke risk was examined (see Appendix 2E-J, which includes forest plots for sensitivity analyses). Thirty-five studies included younger (mean age <65) and 34 included older (mean age ≥65) participants. Risk of stroke with low education was higher in studies that included older participants although this was only significant in studies that reported mean years of education ($X^2(1)=11·08$, $p<0·001$). Use of adjusted versus unadjusted risk ratios, recruitment through hospitals/outpatient clinics, including case-control design, versus population cohorts, stroke ascertainment using clinical examination/neuroimaging versus self-report/centralised health data, participant sex and first only versus recurrent/unspecified stroke, did not explain between-study heterogeneity (Appendix 2E-J).



Footnotes

(1) Adjusted for history of high BP, use of oral contraceptives, marital status, number of live births, cigarette and alcohol consumption, hypertension in pregnancy, family history of premature stroke or AMI,...
(2) Adjusted for history of high BP, use of oral contraceptives, marital status, number of live births, cigarette and alcohol consumption, hypertension in pregnancy, family history of premature stroke or AMI,...
(3) Adjusted for history of high BP, use of oral contraceptives, marital status, number of live births, cigarette and alcohol consumption, hypertension in pregnancy, family history of premature stroke or AMI,...
(4) Adjusted for age,gender and region.
(5) Adjusted for age, sex, race
(6) Adjusted for age. Total number of strokes and controls for education categories used not specified. Total strokes and controls 218 and 1845 respectively.
(7) Adjusted for hypertension, diabetes, hyperlipidemia, previous stroke/TIA, and PAD, current smoking, alcohol abstinence, high alcohol consumption, leisure time sports activity
(8) Adjusted for CHD, hypertension, COPD, obesity, income, age and sex.
(9) Adjusted for age, home ownership, education, smoking, BMI, alcohol, physical activity, depression, marital status, hypertension, diabetes mellitus, heart disease and hysterectomy/oophorectomy
(10) Adjusted for age and sex
(11) Adjusted for age and sex
(12) Adjusted for work related factors on the Job Content Questionnaire, organisational change at the workplace and decreased participation
(13) Adjusted for age and sex
(14) Adjusted for age and sex
(15) Adjusted for age, systolic BP, hypertension, drug use for hypertension, smoking, cardiovascular disease, left ventricular hypertrophy, atrial fibrilation, diabetes, fibrogen, BMI, alcohol consumption
(16) Adjusted for age, systolic BP, hypertension, drug use for hypertension, smoking, cardiovascular disease, left ventricular hypertrophy, atrial fibrilation, diabetes, fibrogen, BMI, alcohol consumption
(17) Adjusted for age, gender, income, medical insurance, smoking and BMI.
(18) Adjusted for age, gender, area of residence, BMI, smoking, alcohol consumption, diabetes, high blood pressure, occupational and leisure time physical activity
(19) Adjusted for hypertension, heart disease, diabetes, smoking

Note: Studies without footnotes report unadjusted results

Figure 2.11A: Educational attainment (low versus high) and risk of stroke, odds ratio, random effects model (OR<1 indicates low education decreases risk of stroke; OR >1 = low education increases risk of stroke)

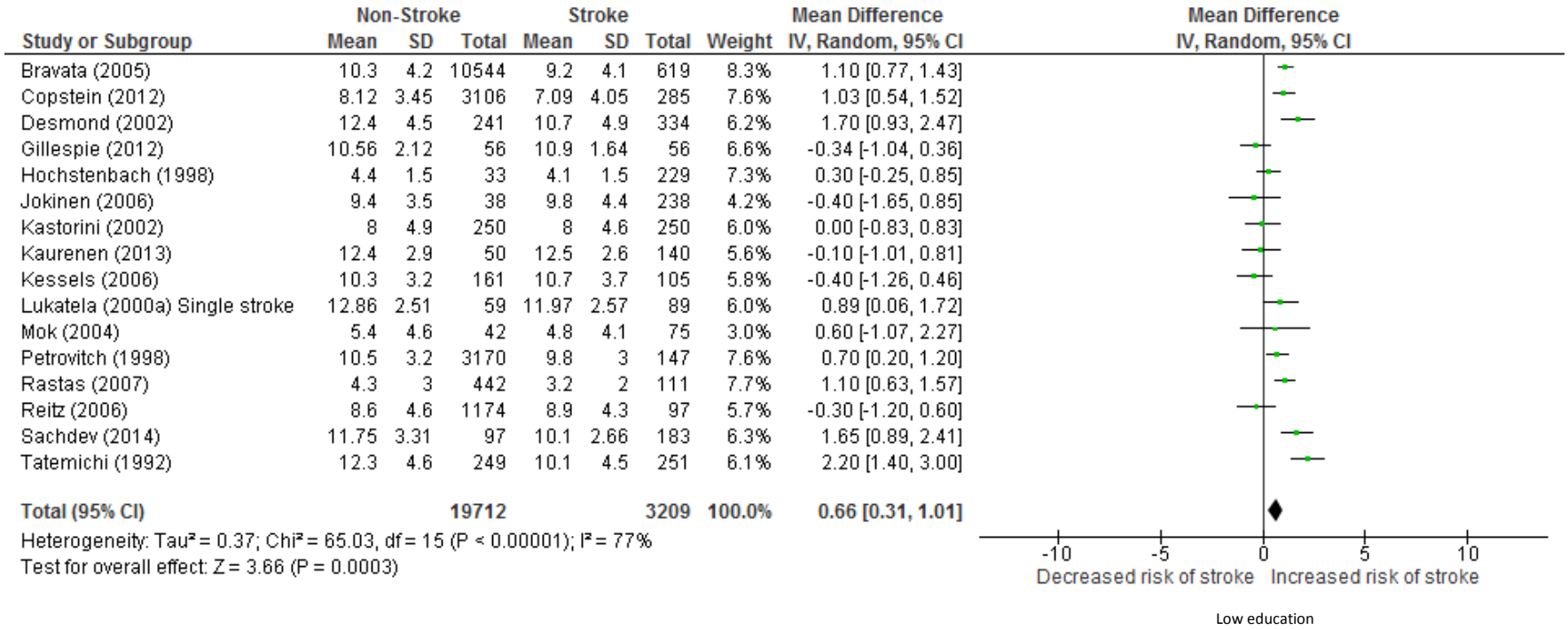
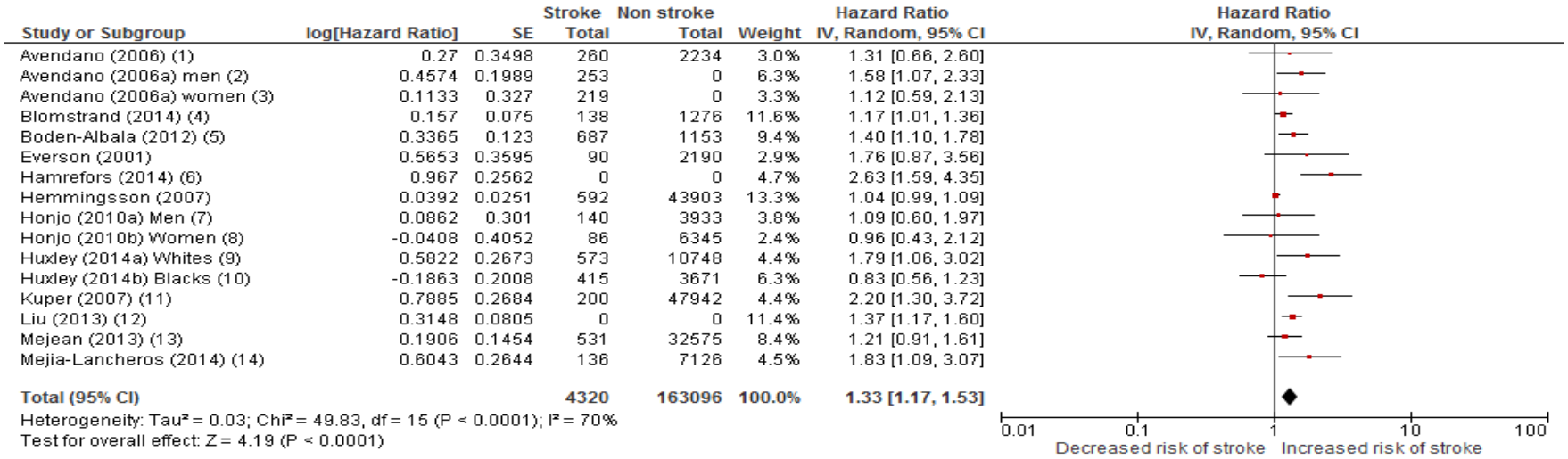


Figure 2.11B: Educational attainment by mean years in persons with and without stroke, random effects model for the mean difference (negative mean difference = lower education decreases risk of stroke and positive mean difference = lower education increases risk of stroke)



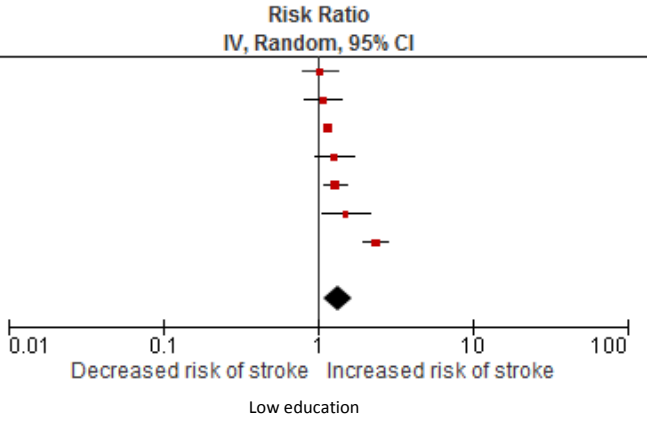
Footnotes

(1) Adjusted for age, sex, race, sex, hypertension, smoking, diabetes, alcohol, BMI, physical activity, social networks, depression, difficult life events
(2) Adjusted for age
(3) Adjusted for age
(4) Adjusted for age, hypertension, BMI, smoking, physical inactivity, cholesterol, tryglycerides, mental stress
(5) Adjusted for cardiac disease, hypertension, diabetes, inactivity, social isolation, Medicaid insurance, home heath aid.
(6) Adjusted for age and sex.
(7) Adjusted for age, area of residence, cholesterol level, physical activity, ethanol intake, marital status, smoking, obesity, medical history of hypertension, diabetes
(8) Adjusted for age, area of residence, cholesterol level, physical activity, ethanol intake, marital status, smoking, obesity, medical history of hypertension, diabetes
(9) Adjusted for age, sex, income, BMI, smoking, systolic blood pressure, antihypertensive medication, diabetes, HDL-C, LDL-C, lipid medication, CHD, PAD, ECG, carotid intima...
(10) Adjusted for age, sex, income, BMI, smoking, systolic blood pressure, antihypertensive medication, diabetes, HDL-C, LDL-C, lipid medication, CHD, PAD, ECG, carotid intima...
(11) Adjusted for age, smoking, BMI, alcohol consumption, hypertension, diabetes, exercise
(12) Adjusted for age, race, ethinicity, gender, marital status, adult SES
(13) Adjusted for age, sex, physical activity, smoking, alcohol consumption, diet
(14) Adjusted for aged, gender, smoking, alcohol consumption, BMI, hypertension, diabetes, high cholesterol, family history of CHD and diet.

Figure 211C: Educational attainment (low vs high) and risk of stroke, hazard ratio, random effects model (Hazard ratio <1 indicates low education decreases risk of stroke; >1 low education increases risk of stroke. Note: Studies without footnotes report unadjusted results.

Study or Subgroup	log[Risk Ratio]	SE	Stroke Total	Non-Stroke Total	Weight	Risk Ratio IV, Random, 95% CI
Gillum (2003a) White males (1)	0.0392	0.1397	318	0	13.5%	1.04 [0.79, 1.37]
Gillum (2003b) White females (2)	0.0862	0.1412	334	0	13.4%	1.09 [0.83, 1.44]
Anderson (2014) (3)	0.1621	0.0183	54048	0	17.3%	1.18 [1.13, 1.22]
Hart (2000) (4)	0.2469	0.1468	416	5757	13.2%	1.28 [0.96, 1.71]
Lindenstrom (1993) (5)	0.2624	0.0852	696	12304	15.7%	1.30 [1.10, 1.54]
Gillum (2003c) Black (6)	0.4187	0.1842	150	0	11.6%	1.52 [1.06, 2.18]
Lisabeth (2007) (7)	0.8671	0.093	631	0	15.4%	2.38 [1.98, 2.86]
Total (95% CI)			**56593**	**18061**	**100.0%**	**1.35 [1.09, 1.67]**

Heterogeneity: Tau² = 0.07; Chi² = 59.45, df = 6 (P < 0.00001); I² = 90%
Test for overall effect: Z = 2.78 (P = 0.005)



Footnotes
(1) Adjusted for baseline age, smoking, history of diabetes, history of heart disease, alcohol consumption, nonrecreational physical activity, blood pressure medication, and systolic...
(2) Adjusted for baseline age, smoking, history of diabetes, history of heart disease, alcohol consumption, nonrecreational physical activity, blood pressure medication, and systolic...
(3) Adjusted for age, sex, calendar year and income
(4) Adjusted for age, smoking,adjusted FEV1, diastolic and systolic blood pressure, height, alocohol consumption and prexisting CHD.
(5) Adjusted for age and sex
(6) Adjusted for baseline age, smoking, history of diabetes, history of heart disease, alcohol consumption, nonrecreational physical activity, blood pressure medication, and systolic...
(7) Adjusted for age, sex and ethinicity

Note: Studies without footnotes report unadjusted results

Figure 2.11D: Educational attainment (low versus high) and relative risk of stroke, random effects model (Risk Ratio<1 indicates low education decreases risk of stroke; Risk Ratio >1 = low education increases risk of stroke).

2.3.2.3 Childhood SES

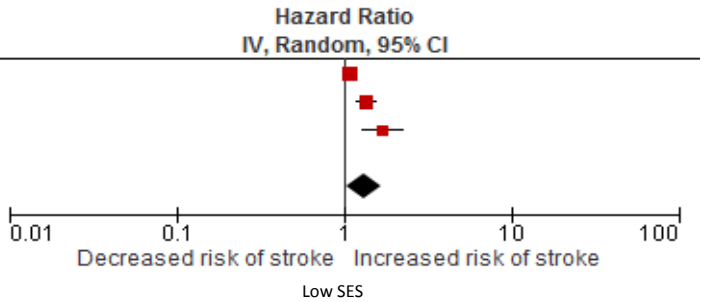
Ten studies, (Wennerstad et al., 2010, Hemmingsson et al., 2007, Grau et al., 2012, Hart et al., 2000, Liu et al., 2013, Lawlor et al., 2006, Johnson et al., 2010, Gliksman et al., 1995, Wannamethee et al., 1996, Kornerup et al., 2010) reported in 15 publications (total n=1,354,899), examined childhood SES and stroke. Over 13,297 stroke and 1,330,496 stroke-free participants were included aged 30-70 years old at the time of follow-up or stroke. One study (Lawlor et al., 2006) did not provide the number of stroke and stroke-free participants (total n=11,106). Frequencies were used to calculate ORs for five studies. (Johnson et al., 2010, Hart et al., 2000, Gliksman et al., 1995, Wannamethee et al., 1996, Wennerstad et al., 2010). One paper adjusted for vascular risk factors (Grau et al., 2012), one for adult SES (Liu et al., 2013) and two for demographic variables. (Liu et al., 2013, Kornerup et al., 2010),

Three studies (Liu et al., 2013, Hemmingsson et al., 2007, Kornerup et al., 2010) reporting HRs (3,240 strokes, 73,644 stroke-free participants) and six (Wennerstad et al., 2010, Grau et al., 2012, Hart et al., 2000, Johnson et al., 2010, Gliksman et al., 1995, Wannamethee et al., 1996) reporting ORs (10,057 strokes, 1,256,852 stroke-free participants) were meta-analysed for childhood SES and stroke. Subjects with lower childhood SES (i.e. father's occupation manual) had an increased risk of stroke compared to those with higher (i.e. non-manual father's occupation) SES (HR=1.32, 95% CI=1.04 to 1.67, p=0.02, I^2 89%; OR=1.28, 95% CI=1.12 to 1.46, p<0.001, I^2 55%; Figure 2.12A-B). Removal of one large study (Gliksman et al., 1995) reduced the heterogeneity substantially (OR=1.36, 95% CI=1.30 to 1.42, p<0·0001, I^2=0%).

One paper (Lawlor et al., 2006) reported the stroke rate by 10,000 person years by father's occupational class so could not be meta-analysed, but showed that lower versus higher father's occupational class was associated with a higher stroke rate (7.8 per 10,000/year versus 2.3 per 10,000/year, p=0.001).

Study or Subgroup	log[Hazard Ratio]	SE	Stroke Total	No stroke Total	Weight	Hazard Ratio IV, Random, 95% CI
Hemmingsson (2007)	0.077	0.0242	592	43903	39.3%	1.08 [1.03, 1.13]
Liu (2013) (1)	0.3075	0.0724	2298	20549	35.0%	1.36 [1.18, 1.57]
Kornerup (2010) (2)	0.5365	0.1438	350	9192	25.7%	1.71 [1.29, 2.27]
Total (95% CI)			**3240**	**73644**	**100.0%**	**1.32 [1.04, 1.67]**

Heterogeneity: Tau² = 0.04; Chi² = 18.10, df = 2 (P = 0.0001); I² = 89%
Test for overall effect: Z = 2.25 (P = 0.02)

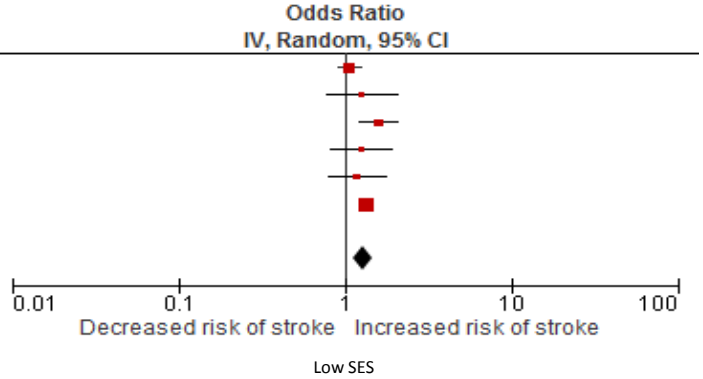


Footnotes
(1) Adjusted for age, race, ethnicity, gender, marital status, adulthood SES, smoking status, body mass index and chronic conditions.
(2) SES defined by financial problems in childhood. Adjusted for age and sex

Figure 2.12A: Childhood socioeconomic status (low versus high) and risk of stroke, hazard ratio, random effects model (Hazard Ratio<1 indicates low SES decreases risk of stroke; >1 = low SES increases risk of stroke).

Study or Subgroup	log[Odds Ratio]	SE	Stroke Total	Non-stroke Total	Weight	Odds Ratio IV, Random, 95% CI
Gliksman (1995)	0.0677	0.0771	828	116178	25.8%	1.07 [0.92, 1.24]
Grau (2012) (1)	0.2357	0.2542	370	370	6.0%	1.27 [0.77, 2.08]
Hart (2000)	0.4699	0.136	404	5249	15.1%	1.60 [1.23, 2.09]
Johnson (2010) (2)	0.2264	0.2205	104	2507	7.6%	1.25 [0.81, 1.93]
Wannamethee (1996)	0.1655	0.2047	136	5380	8.6%	1.18 [0.79, 1.76]
Wennerstad (2010)	0.3075	0.023	8215	1127168	36.9%	1.36 [1.30, 1.42]
Total (95% CI)			**10057**	**1256852**	**100.0%**	**1.28 [1.12, 1.46]**

Heterogeneity: Tau² = 0.01; Chi² = 11.14, df = 5 (P = 0.05); I² = 55%
Test for overall effect: Z = 3.65 (P = 0.0003)



Footnotes
(1) Adjusted for hypertension, diabetes, hyperlipidemia, previous stroke/TIA, PAD, smoking, alcohol abstinence and consumption and leisure time sports activity
(2) SES defined by Father's highest level of education

Figure 2.12B: Childhood socioeconomic status (low versus high) and risk of stroke, odds ratio, random effects model

2.3.3 Early life risk factors for post-stroke depression

Thirty three articles were identified, all examining education and post stroke depression (see table 2.3 for summary and Appendix 2D for full details of included papers). One of these articles (Brodaty et al., 2007) also examined premorbid cognition. There were no studies examining childhood SES and post-stroke depression.

Table 2.3: Table of studies included in systematic review of early life factors and post-stroke depression.

	Childhood IQ	**Education**	**Childhood SES**
Number of papers identified	1	33	0
Number of studies included	1	33	0
Study setting			
Population	0	3	0
Hospital	1	22	0
Community	0	1	0
Outpatient clinic	0	7	0
Total number of participants	205	8,377	0
Total number of depressed patients	37[a]	2,664	0
Total number of non-depressed patients	98[a]	5,460	0
Age range of included studies	72-73	27-85	0
Quality score[b]	20	20 (1.5)	NA
Range	NA	18-23	NA

[a] Data not reported for 2 studies

[b] Median (interquartile range)

SES: socioeconomic status

Quality assessment and publication bias

The quality of the included papers was good, with scores from 18-23/24 (median=20). The main risk of bias was regarding sample representativeness (figure 2.13).

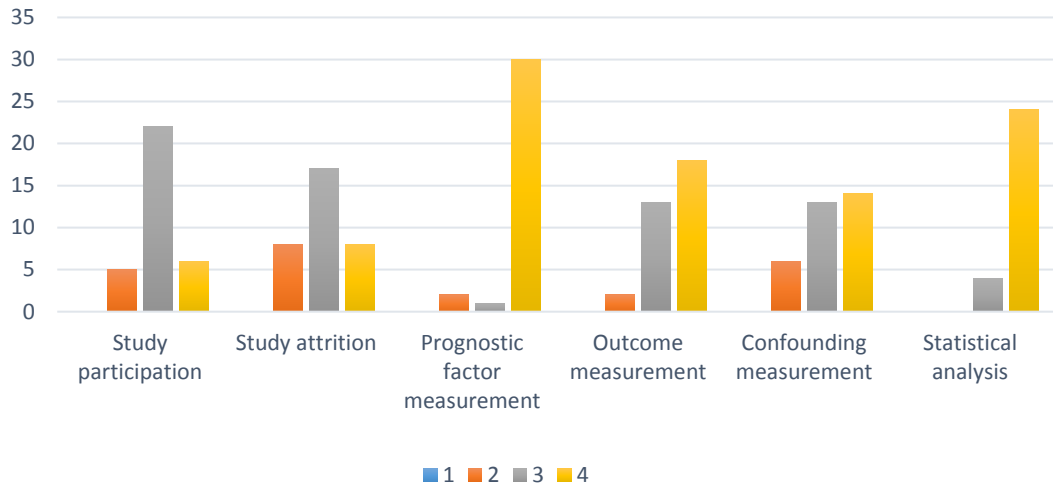
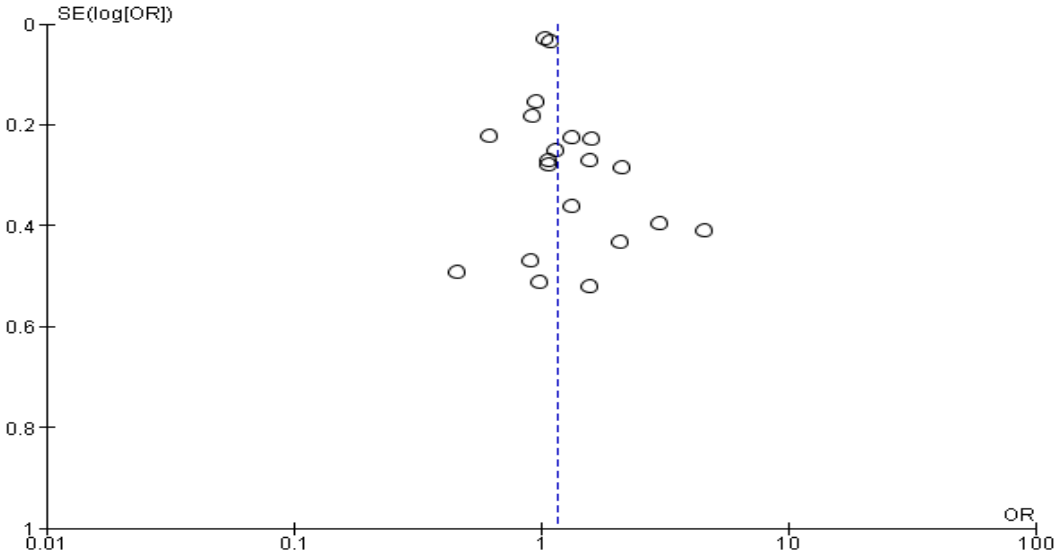


Figure 2.13: Quality assessment for studies examining early life factors and post-stroke depression: Frequencies of scores on individual quality items.

Egger's regression test showed evidence of publication bias among papers examining education level and depression (Figure 2.14). Due to the small number of studies, it was not possible to assess publication bias in papers reporting mean years of education or correlation coefficients.



Egger's regression: t= 15.89, p<0.001

Figure 2.14: Publication bias of studies examining education and post-stroke depression

2.3.3.1 Premorbid IQ

One paper (Brodaty et al., 2007) (n=205) examined premorbid IQ using the National Adult Reading Test Revised (NART-R) and post-stroke depression diagnosed using The Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (37 post-stroke depression; 98 no depression). NART scores, transformed into an IQ score, were higher (better premorbid IQ) in those without depression (mean: 104.0, SD 10.1) compared to those with post-stroke depression (mean: 101.8, SD 9.8) but this difference was not statistically significant.

2.3.3.2 Education

Thirty three studies (n=8,377) examined education and post-stroke depression (2,664 post-stroke depression; 5,460 no depression participants, 314 participants not classified) aged 27-85 at follow up. Education level was assessed as duration (i.e. <=8 years vs >8 years) in 12 studies, attainment (i.e. <High School vs ≥High school) in 13 studies and mean years of education in 8 studies (Brodaty et al., 2007, Choi-Kwon et al., 2012, Kim and Choi-Kwon, 2000, Snaphaan et al., 2009, Starkstein et al., 1993, Tang et al., 2005, Tateno et al., 2002, Tene et al., 2016). Most studies were conducted in Europe or North America (17 studies) however some were based in the Asia Pacific Region (12 studies), Africa (1 study), the Middle East (2 studies) and South America (1 study). Twenty three studies were based in hospitals, 6 were outpatient studies and 4 were population or community based studies.

Education level and depression

Eight papers (Altieri et al., 2012, Naess et al., 2005, Paolucci et al., 1999, Paul et al., 2013, Schepers et al., 2009, Sienkiewicz-Jarosz et al., 2010, Tang et al., 2011, van de Port I.G.L. et al., 2007) (n=1785) reported ORs (711 with and 1074 without post-stroke depression) and 12 papers (n=3879) reported frequencies of presence of post-stroke depression by educational attainment or duration (1434 with and 2445 without post-stroke depression) which were used to calculate unadjusted ORs. Three studies (Paolucci et al., 1999, Paul et al., 2013, Tang et al., 2011) reported adjusted odds ratios.

Four studies (Altieri et al., 2012, Paolucci et al., 2006, Shi et al., 2015, Vataja et al., 2001) classified participants with depression by a diagnosis of major depressive

disorder (MDD) according to DSM criteria. Two studies (Schepers et al., 2009, van de Port I.G.L. et al., 2007) used the Centre for Epidemiologic Studies Depression scale (CES-D) which diagnoses a depressive episode using the DSM criteria. The remaining studies defined participants with depressive symptoms according to scores on depression rating scales including the Montgomery Asberg Depression Rating Scale (MADRAS) (4 studies (Jiang et al., 2014, Naess et al., 2005, Nys et al., 2006, Verdelho et al., 2004) score ≥7 mild depressive symptoms), the Hamilton Depression Rating Scale (HDRS) (3 studies (Li et al., 2002, Paolucci et al., 1999, Zhang et al., 2005) score ≥8 mild depressive symptoms, 1 study (Paolucci et al., 1999) ≥21 severe depressive symptoms), the Becks Depression Inventory (BDI) (2 studies (Berg et al., 2001, Fatoye et al., 2009); score ≥10 mild depressive symptoms), the Geriatric Depression scale (GDS) (3 studies; Bengali version (Paul et al., 2013): score ≥21 severe depression; Short version (Sienkiewicz-Jarosz et al., 2010) : score >5, short version ≥7 (Tang et al., 2011), the Patient Health Questionnaire 8 (PHQ-8) (1 study (Hirata et al., 2016)); score ≥10 moderate depressive symptoms) and a Chinese self-report depression scale (1 study (Zhang et al., 2009)).

Overall low education (<9 years) was associated with increased risk of post-stroke depression (OR 1.16 95% CI 1.03-1.31, p=0.01, figure 2.15).

Heterogeneity between studies was moderate (I^2 58%).

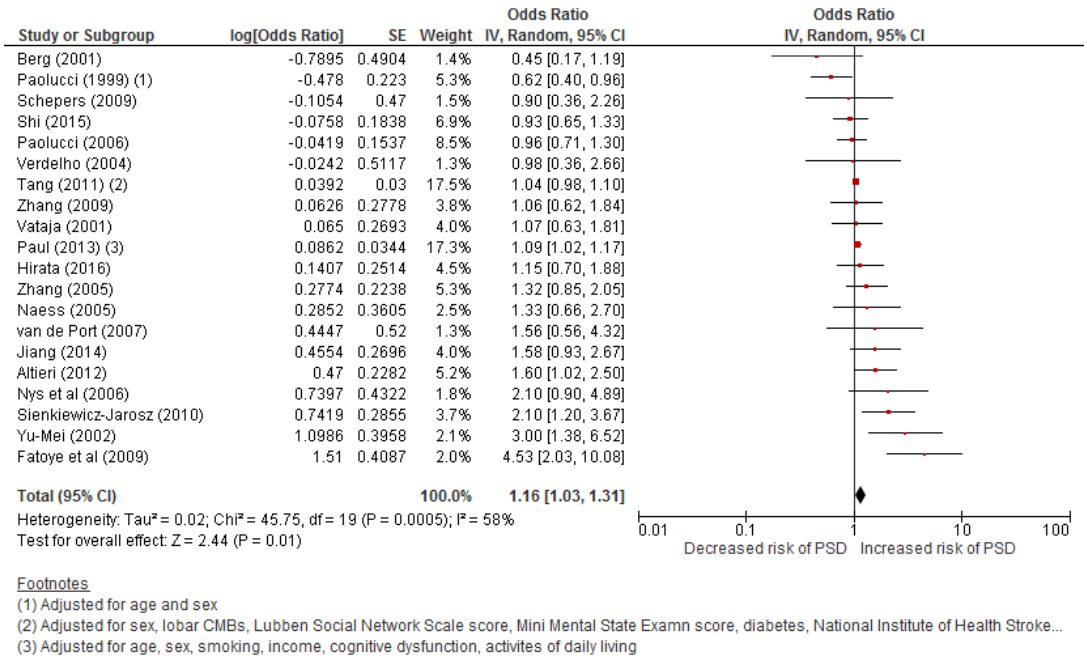


Figure 2.15: Forest plot comparing low vs high education and risk of depressive symptoms following stroke.

Sensitivity analysis

Several post hoc sensitivity analyses were conducted examining education level and post-stroke depression (see appendix 2K-R which includes forest plots for sensitivity analyses). Severity of depression explained some of the variance in post-stroke depression ($\chi^2(1) = 4.47$ p=0.03): low education was associated with increased risk of mild depression or depressive symptoms and above (n= 2,133 OR 1.47 95% CI 1.10-1.97, p<0.01) but not major depression or severe depressive symptoms only (n= 3,754 OR 1.04 95% CI 0.90-1.20, p=0.60). However, the risk of post-stroke depression did not differ according to the depression scale used, participants age (<65 vs ≥65 years), first stroke only vs recurrent or unspecified stroke, past history of depression as an exclusion criteria (yes vs no), time since stroke (<= 6 months vs >6 months), study setting (hospital or outpatient clinic vs population-based) and country of origin (Europe or North America vs Asia Pacific region or Africa).

Exclusion of the paper (Zhang et al., 2005) with the lowest quality score, or the two studies (Naess et al., 2005, Verdelho et al., 2004) with unclear definitions of education levels, did not significantly alter the results (OR 1.23, 95% CI 1.02-1.49, p=0.03; OR 1.24, 95% CI 1.03-1.50, p=0.02).

Mean years of education and depression

Seven studies (Brodaty et al., 2007, Choi-Kwon et al., 2012, Kim and Choi-Kwon, 2000, Starkstein et al., 1993, Tang et al., 2005, Tateno et al., 2002, Tene et al., 2016) (n=1943) reported mean years of education for participants with and without post-stroke depression (273 post-stroke depression and 1251 no post-stroke depression) and one study (Snaphaan et al., 2009) reported median years of education. Post-stroke depression was diagnosed using the DSM criteria (5 studies (Brodaty et al., 2007, Kim and Choi-Kwon, 2000, Starkstein et al., 1993, Tang et al., 2005, Tateno et al., 2002)), and the BDI (Choi-Kwon et al., 2012), the GDS (Tene et al., 2016) and the Hospital Anxiety and Depression Scale (HADS) (Snaphaan et al., 2009) in one study each. Participants with post-stroke depression had significantly fewer years of education than those without post-stroke depression (MD 0.68 95% CI 0.05-1.31 p=0.03, Figure 2.16). None of these papers adjusted for vascular risk factors.

Heterogeneity between studies was moderate (I^2 56%).

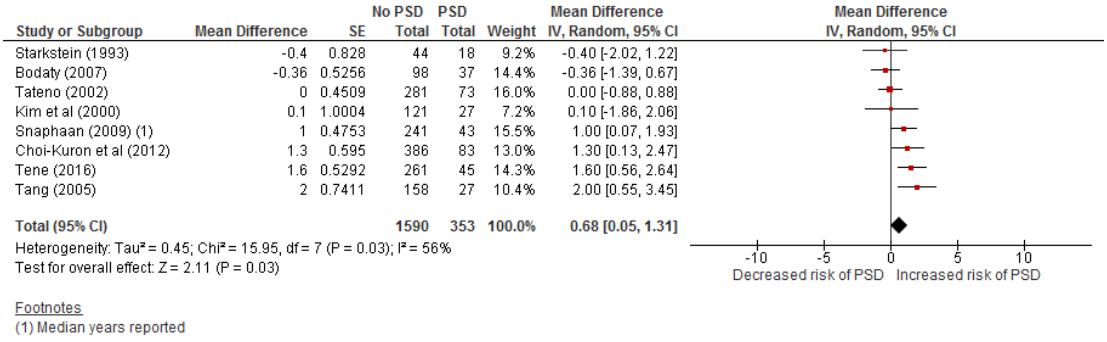


Figure 2.16: Mean years of education for those with and without post-stroke depression.

Random effects model for the mean difference. Negative mean difference= lower education decreases risk of post-stroke depression and positive mean difference= higher education decreases risk of post-stroke depression.

Correlation between education and depressive symptoms

Of the 33 studies, five (Carod-Artal et al., 2009, Donnellan et al., 2016, Schreiner et al., 2001, Spalletta et al., 2002, Visser et al., 2014) (n= 831) reported correlation coefficients for education and post-stroke depressive symptoms at age 56-70. Most studies used years of education while one (Visser et al., 2014) used educational attainment ranging from 1 (Primary school) to 7 (University degree). One study (Visser et al., 2014) provided risk factor adjusted results. Depressive symptoms were

measured using the HADS in two studies (Carod-Artal et al., 2009, Donnellan et al., 2016), the HDRS (Spalletta et al., 2002), the GDS (Schreiner et al., 2001) and the CES-D (Visser et al., 2014) in one study each.

Overall correlation between education and depressive symptoms did not reach statistical significance (r= -0.10 95% CI -0.24-0.04, p=0.15, figure 2.17), although the effect was in the same direction as the effect of the alternative education measures above on post-stroke depression. Heterogeneity was high between studies (I^2 77.3%) but the data were too sparse for sensitivity analyses.

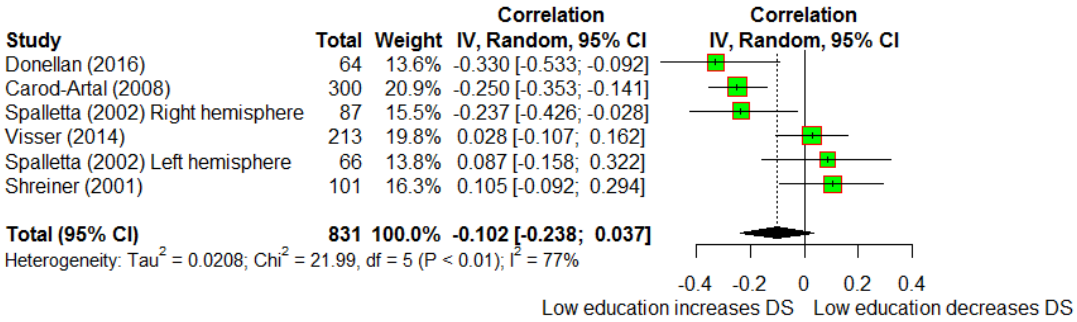


Figure 2.17: Forest plot showing correlation between education and depressive symptoms in stroke patients. Negative correlation= low education increases depressive symptoms; Positive correlation= low education decreases depressive symptoms. DS= depressive symptoms.

2.3 Discussion

This meta-analysis is the first comprehensive examination of all data on childhood IQ, education and childhood SES and risk of subclinical CVD, stroke and post-stroke depression. It suggests that longer duration of education predict lower risk of subclinical CVD, clinical stroke and post stroke depression in later life. Less versus more education was associated with a 17% relative increase in risk of subclinical CVD, a 35% relative increase in risk of stroke and a 16% relative increase in risk of post-stroke depression. This relative risk translates to an absolute increase in stroke risk of approximately 3.5/1,000 for lower versus higher education. When expressed as whole number this means for every 2,000 people who only completed education up to high school level (11 years), 7 more will have a stroke compared with people with college education (> 11 years). For post-stroke depression this relative risk translates to an absolute increase in post-stroke depression risk of approximately 5.9/1,000 for lower versus higher education but with wide confidence intervals and heterogeneity. Furthermore, participants with stroke and post-stroke depression had an average of 0.66 and 0.68 fewer years of education respectively than those without stroke and post-stroke depression. These findings further suggest that higher cognitive ability in childhood and higher SES are associated with lower risk of subclinical CVD and clinical stroke. Although only one study examined childhood SES and risk of subclinical CVD. Lower childhood SES and IQ were each associated with about a 17- 32% relative increase in risk of stroke, and there was statistically significant correlation between childhood IQ and WMH burden in later life.

There was considerable heterogeneity between studies examining risk of stroke and post-stroke depression. Sensitivity analyses for the stroke papers showed that risk factor adjustment, population vs hospital-based, and stroke ascertainment method did not explain heterogeneity. Stroke risk was higher and the relationship to education stronger in studies including older versus younger participants. Heterogeneity between studies examining post-stroke depression was partly explained in sensitivity analyses by difference in the severity of depression being measured. Low education level had a stronger effect on mild depressive symptoms and above compared to MDD or severe depressive symptoms only. The diagnosis of depression in stroke populations is more difficult than in those without stroke and many depression scales were not originally developed for patients with stroke. Stroke patients may suffer from symptoms such as fatigue and lack of appetite after stroke, which may lead to inflated

scores on depression scales containing a somatic component (e.g. BDI, HDRS) compared to those that do not include such items (e.g. HADS, MADRAS). No studies adjusted for other common associates of post-stroke depression such as fatigue, although these factors should be considered when conducting research into post-stroke depression. Meta-analysis (Meader et al., 2013) suggests that the CES-D, HDRS and PHQ-9 are the most promising options to screen for post-stroke depression. However in this review CES-D and the HDRS were only used in three (Schepers et al., 2009, van de Port I.G.L. et al., 2007, Visser et al., 2014) and four (Li et al., 2002, Paolucci et al., 1999, Zhang et al., 2005) studies respectively. One study (Hirata et al., 2016) used the PHQ-8 which contains one less question that the PHQ-9.

The literature had several limitations. Firstly, confounders such as adult SES and vascular risk factors were poorly addressed, either because authors reported unadjusted results or because frequency data were used to calculate unadjusted odds ratios. In those papers that did include adjustment for confounders (2 studies on subclinical CVD; 7 studies on stroke; 4 studies on post-stroke depression), there was variation in the number and type used. No studies adjusted for other early life factors and only one study adjusted for adult SES. Although the latter is likely to influence later life CVD. Due to the small number of papers it was not possible to compare adjusted and unadjusted odds ratios in papers examining subclinical CVD or post-stroke depression. For papers examining stroke risk adjusting for known risk factors showed a lower stroke risk compared to unadjusted results. However, the overall effect was still significant.

Secondly many studies included relatively young participants yet risk of subclinical CVD and stroke increases with age. The magnitude of early life effects on CVD may therefore have been underestimated. In sensitivity analyses, the stroke risk was higher and the relationship to education stronger in studies including older versus younger participants. However the association between education and post-stroke depression was the same for older versus younger participants.

Thirdly, differences in definitions of markers of subclinical CVD and differences in the ascertainment of stroke may have affected results and may explain some of the observed heterogeneity between studies. Few studies provided clear working definitions of subclinical CVD. Cortical and subcortical infarcts were not distinguished (two studies (Mortamais et al., 2014, Tsukishima et al., 2001) nor were symptomatic

or asymptomatic infarcts (two studies (Brayne et al., 2010, Elkins et al., 2006). However, on balance, these infarcts appeared likely to be asymptomatic and their omission did not influence the results. Lack of consistency in the definitions of CVD features may have resulted in similar lesions being classified differently across studies, hence the focus on overall CVD. Use of published standards for reporting vascular findings on neuroimaging (Wardlaw et al., 2013) should facilitate future meta-analyses of imaging CVD. Many larger studies examining risk of stroke used centralised health statistics to diagnose history of stroke which may be less reliable than using clinical examination and neuroimaging. In the sensitivity analysis studies using centralized health statistics showed a lower risk of stroke compared to those using clinical examination and neuroimaging.

Fourthly, in studies examining post-stroke depression exclusion criteria varied among studies. Seven studies excluded participants with a pre-stroke history of depression and eight studies excluded participants with a previous history of stroke, both factors which have been identified as risk factors for post-stroke depression (De Ryck et al., 2014) . The sensitivity analyses showed that studies including participants with a history of stroke or depression reported a higher effect of education on post-stroke depression risk than those that excluded such participants, but these differences were not significant. No studies adjusted for history of depression or stroke in their analysis.

Finally, the majority of studies were from Europe or North America followed by the Asia Pacific Region. Sensitivity analysis in studies examining post-stroke depression found no difference between studies conducted in Europe or North America compared to the Asia Pacific Region or Africa. However, sensitivity analysis were only conducted on a subset of papers and social and educational disparities may vary between these world regions.

The funnel plots and Egger's regression identified possible publication bias which may have influenced the results. Unlike clinical trials observational studies are not often registered, and analyses may be performed and not published. Furthermore, some studies may not report all collected data (e.g. omit some neuroimaging variables). If negative studies are unpublished, the relationship between early factors and CVD and depression will have been overestimated. However, many of the studies collected early life factors, particularly education, as a descriptive statistic, which may have reduced the likelihood of publication bias. Studies with less than 50 participants were excluded as results from small studies can be less reliable (Button et al., 2013).

Therefore smaller non-significant studies may have been excluded which may have contributed to the asymmetrical funnel plots.

It is likely that education is interrelated with premorbid IQ and that all factors are associated with an increased risk of CVD and depression. However only two papers, both examining risk of stroke, accounted for other early life factors in their analysis (Wennerstad et al., 2010, Hemmingsson et al., 2007). These studies found that the relationship between lower IQ in early adulthood and increased risk of stroke in middle-age men remained when controlled for education. Other studies suggest that there is a strong association between childhood IQ and later life disease risk even when accounting for factors including childhood SES (Hart et al., 2000, Lawlor et al., 2008).One paper reported a significant direct effect of childhood SES on WMH burden with no mediation by childhood IQ or education (Murray et al., 2014), but no other studies on subclinical CVD included more than one early life factor. Another study (Farfel et al., 2013) reported that exposure to minimal amounts of schooling (1-4 years) appeared to be protective against development of subclinical CVD. This suggests that although reciprocal pathways between IQ, SES and education are likely to be important, there may also be independent influences on later health. Education is also strongly associated with adult SES which is itself a risk factor for subclinical CVD, stroke and depression (Marshall et al., 2015). Future studies should examine associations between education and CVD and post-stroke depression when controlling for other early life factors

2.3.2 Strengths and limitations of the review

This systematic review had limitations. It was not possible to contact all authors for missing data due to lack of resources. Three early life factors were specified to review and studies on other, potentially relevant, influences (e.g. birth weight, nutrition) were not included. Classification of WMH and SVD varied between studies, as did diagnosis of post-stroke depression (low vs high or absent vs present), which may affect data interpretation. The sensitivity analysis was not able to account for all the heterogeneity. It was not possible to correct for adult SES or lifestyle as this information was not available. However, others have found that effects of childhood influences on overall mortality persist after correction for adult SES giving no reason to think that the childhood influences seen here are solely due to unmeasured adult influences (Juárez et al., 2016).

Strengths of the review include a pre-specified published protocol, validated search strategy, double data extraction. Published guidelines and used exemplary methods on conduct of systematic reviews and meta-analyses were followed, and an established scale for quality assessment was used which showed an overall high level of study quality. Some sample sizes were small, however there was a reasonable total sample size for many of the analyses producing a comprehensive literature review and meta-analyses amassing data on over 5,000,000 participants. Some analyses lacked power and therefore some significant associations may have been missed.

2.3.3 Implications and conclusions

Positive early life factors can influence occupation, increase access to health care, influence health literacy, disease self-management and prevention. They may influence behaviours conducive to health e.g. healthy eating and reduce negative behaviours e.g. smoking. This may in turn influence self-management of vascular risk factors (e.g. hypertension, obesity). Alternatively, education and IQ may reflect brain integrity or resilience (Penke et al., 2012): white matter structural integrity is better and the cortex is thicker in 70 year olds who scored higher on IQ tests at age 11, which may protect against accumulating CVD (Deary and Johnson, 2010, Karama et al., 2014), hence reduce the risk of stroke and dementia (Debette and Markus, 2010). These possibilities remain to be tested.

The findings from this systematic review show a consistent association between low education and increased risk of subclinical CVD, stroke and post-stroke depression. They also show that low childhood IQ and low childhood SES are associated with an increased risk of subclinical CVD and stroke. All subclinical features assessed here, stroke and post-stroke depression increase risks of cognitive decline and dementia. cSVD increases risk of stroke and depression independently worsens chances of recovery after stroke. Health disparities have been widely discussed and emphasise the importance of addressing social inequality to improve health outcomes (Marmot and Bell). That the effects of such disparities appear to persist across decades of life highlights the importance of identifying modifiable factors which may be targets for future social policy interventions. The results of this meta-analysis support the view that access to quality education may reduce cerebrovascular disease and improve population health in later life. Efforts to understand factors which may contribute to late life brain health, from the earliest stages in life, are important targets for future

research and public health policy. Future studies should examine the combined effects of intelligence, SES and education to determine the independent contribution of each factor to CVD and depression (and dementia) in later life.

3. Methods

This thesis uses data collected from participants from the STRADL cohort, the Dutch Famine Birth Cohort, the Lothian Birth Cohort 1936 and the Simpson cohort. These are four longitudinal cohort studies which have data from birth and childhood and imaging and neuropsychiatric data collected in later life. These datasets will be introduced in the following sections and full details of the participant demographics will be described in the context of each analysis in Chapters 4, 5 and 6. They will vary depending on which variables are included in each analysis. Table 1 provides a summary of the different follow up periods for each cohort

3.1 Participants

Table 3.1: Summary of data collected in all four cohorts

Cohort	Year of birth	Data collection		Purpose (s) of study
		Year	Age	
STRADL	1950-1956	1962-1964 (ACDS)	7-11 years	Survey of the prevalence of mental disability in primary school children and how this relates to obstetric, perinatal and social factors.
		1998 (ACONF)	43-49 years	Examine morbidity and health related behaviours in surviving ACDS participants.
		2006-2011 (GS:SFHS)	51-57 years	Identify genetic basis of common complex diseases.
		2015-present	59-65 years	Investigate the aetiology of major depressive disorder.
Dutch Famine Birth cohort	1943-1947	1995-1997	50 years	Examine the effect of prenatal famine exposure on glucose tolerance, BMI and insulin profile in adult offspring.
		2002-2004	58 years	Examine the effect of variations in the composition of the maternal diet on blood pressure in adult offspring.
		2008-2009	65 years	Examine the effect of prenatal famine on HPA function and psychological stress response in adult offspring.
		2012	68 years	Examine the effect of prenatal famine exposure on age related changes in the brain using MRI.
LBC 1936	1936	1947	11 years	Assess IQ of school children in Scotland.
		2004-2007	69.5 years	Understand the genetic, physiological and psychological factors involved in aging.
		2007/2010	72.5 years	Understand the mechanisms responsible for white matter damage and the effect of cognitive function.
		2011-2014	75.5 years	Examine determinants and consequences of age related changes in brain structure using longitudinal brain imaging data.
		2015-present	78.5 years	Examine determinants and consequences of age related changes in brain structure using longitudinal brain imaging data.
The Simpson cohort	1921-1926	1932 (LBC 1921 only)	11 years	Assess IQ of school children in Scotland.
		2000	75-82 years	Investigate relationships between birth measurements and brain structure and cognitive function in later life.

3.1.1 Stratifying Resilience and Depression Longitudinally (STRADL)

The STRADL study (Navrady et al., 2018) began in 2015 and aimed to investigate psychological resilience and identify causal mechanisms and pathways of depression subtypes. STRADL sought to re-contact participants from Generation Scotland: Scottish Family Health Study (GS: SFHS) (Smith et al., 2013, Smith et al., 2006) to complete additional assessment of mental health. GS: SFHS is a family based cohort of over 24,000 participants who have provided samples (blood, saliva and urine) and data for genetic epidemiology research, with most consenting to record linkage and recontact. To be eligible for STRADL GS:SFHS participants must have given permission for recontact, have a community health index (CHI) number and be living in Scotland. A total of 21,525 (89%) of GS:SFHS members were eligible for STRADL.

Initial comparison of STRADL participants with the GS: SFHS cohort shows that STRADL participants appear to be older, predominantly female and from less socioeconomically deprived areas that GS: SFHS cohort as a whole (Navrady et al., 2018) .

Among participants in GS: SFHS are members of the Aberdeen Children of the 1950s cohort (Batty et al., 2004) (see Figure 3.1). This thesis will use data from participants who have early life data collected as part of ACONF and later life imaging and neuropsychiatric data collected as part of the STRADL study.

3.1.1.1 Aberdeen Children of the 1950's.

The Aberdeen Children of the 1950's (ACONF) consists of 12,150 individuals born between 1950 and 1956 who were attending primary schools in Aberdeen, Scotland in 1962. Between 1962 and 1964 14,939 children, aged approximately 7-11 years, took part in the Aberdeen Child Development Survey (ACDS). This was a cross sectional survey conducted to determine the prevalence of metal disability in Aberdeen primary school children. The study involved administration of a series of reading tests and extraction of retrospective routinely collected educational test results. Medical data was also collected and obstetric and perinatal records were obtained from the Aberdeen Maternity Hospital where a large proportion of the births in the city took place. This allowed examination of associations between perinatal and social factors and child development. Further details of these factors are presented in section 3.2.

In 1998 researchers began to trace surviving members of the cohort. Names and dates of birth were taken from the original 1962 ACDS data and The National Health Service Central Register was used to determine whether participants were alive and if so where they were currently living. Of the 12,150 subjects 99% (12,013) were traced. Health data were collected through linkage with routinely collected data from the Scottish Morbidity Record and provided by the Information Statistics Division (ISD) of the National Health Services Scotland. This included morbidity for a range of outcomes including diagnosis of CVD, schizophrenia and breast cancer. Perinatal information of babies born to female study members in Scotland between 1967 and 1999 was also collected using Scottish maternity discharge records and the Aberdeen Maternity and Neonatal Databank. Additional information was obtained using a postal questionnaire which was administered between 2001 and 2003. The questionnaire was sent to all subjects with an address in Scotland, England or Wales and contained questions regarding occupation, living conditions, height, weight, health and health related behaviours. It achieved a response rate of 64% (7183) with higher childhood cognitive scores and non-manual social class at birth associated with higher response rates.

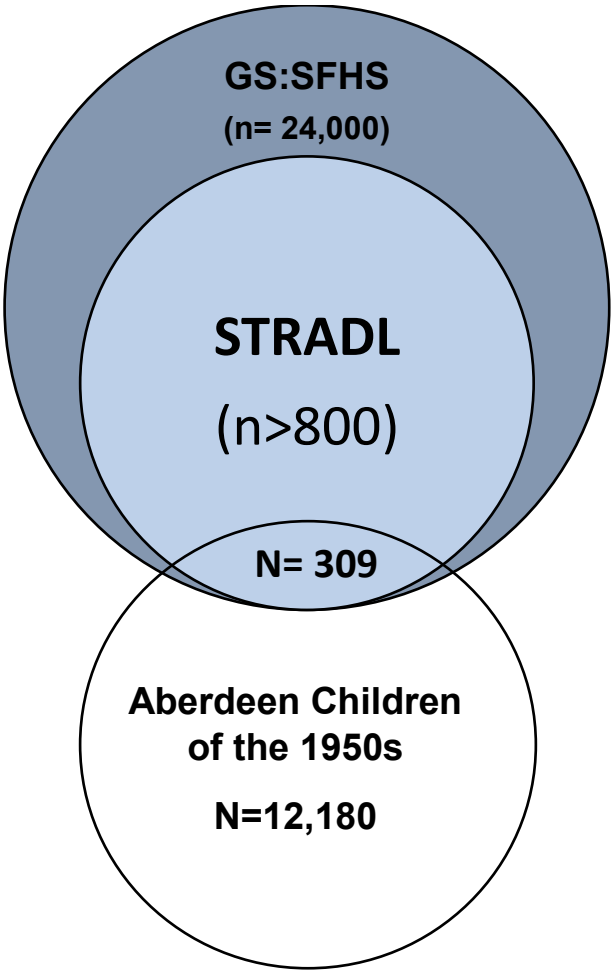


Figure 3.1: STRADL recruitment in relation to Generation Scotland and ACONF

3.1.1.2 Sample selection

At the start of STRADL, in 2015, 557 ACONF participants who were members of GS: SFHS and who had consented to be recontacted were invited to participate in STRADL. 331 people agreed, 90 people declined and 136 people didn't respond (Figure 2)

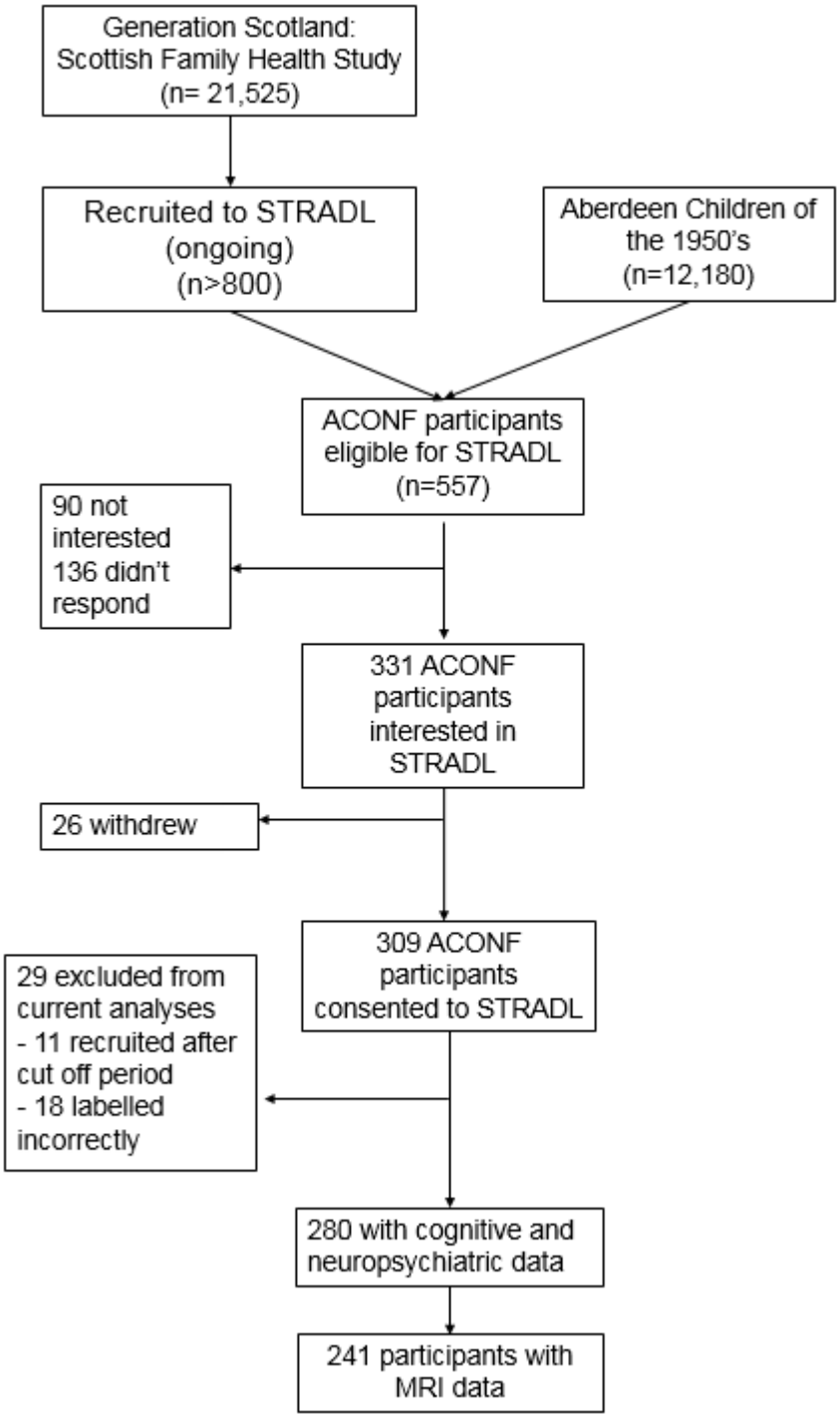


Figure 3.2: Flow chart of STRADL recruitment

Of the 331 people who agreed to participate in STRADL 26 people later withdrew which left 309 members of ACONF who attended appointments and completed demographic and neuropsychiatric assessments. Further details of these assessments are given in section 3.2. Of these 309 participants, 11 were recruited

after the cut off period and 18 participants were labelled incorrectly at their initial assessment. This mislabelling meant it was not possible to link these participants' data to their original ACONF identifier. Therefore these participants have been excluded from the analyses in this Thesis. This left 280 participants with demographic and neuropsychiatric data. 241 participants also completed MRI scans.

3.1.2 Dutch Famine Birth cohort

The Dutch famine of 1944-45, also known as the 'Hunger Winter', occurred in German occupied Netherlands at the end of the Second World War. By September 1944 Allied troops had liberated most of Southern Netherlands but much of the north of the country remained occupied. The Dutch government, who were in exile in London, called for a national railway strike to further the Allied liberation efforts. In retaliation the German authorities put an embargo on all food transports to the occupied West of the country which included Amsterdam. This embargo was partially lifted in November 1944, however a shortage of fuel and one of the harshest winters on record made food transportation over water difficult. This led to a severe 5 month famine in the cities of western Netherlands. In May 1945 the western part of the Netherlands was liberated by allied forces and the famine came to an end. The famine resulted in the deaths of approximately 30,000 civilians and affected people of all social classes.

Nutrition in the Netherlands had generally been adequate up until October 1944 and food supplies were restored immediately after liberation on May 5th 1945. Therefore, although a humanitarian disaster, the Dutch famine provides a unique opportunity to examine the effects of maternal undernutrition during specific gestational windows on subsequent adult health.

3.1.2.1 Selection procedure

The first investigators to study the long term consequences of undernutrition on children conceived during the Dutch famine, analysed military conscription records from over 400,000 men examined at age 18. The aim of these studies, which were conducted in the 1970s, was to examine the effects of intrauterine exposure to famine on mental and physical health in early adulthood by comparing the records of exposed and unexposed men (Stein et al., 1975, Stein et al., 1972).

The Dutch Famine Birth Cohort was formed between 1994 and 1996.(Ravelli et al., 1998) These later studies used the detailed prenatal and birth records of babies born

in Amsterdam around the time of the famine to study the course of the pregnancy and perinatal factors and their effect on adult health. A flow chart of the recruitment process is presented in Figure 3.4. Researchers identified 5425 people born between November 1943 and February 1947 in the Wilhelmina Gasthuis hospital in Amsterdam all of whom had detailed birth records. Medical records for 2680 of these individuals were obtained from the Gemeentearchief (city archive) of Amsterdam. All were live born singletons born between November 1st 1943 and February 28th 1947. 1380 individuals were born between 1st November 1944 and 28th February 1946 and were therefore exposed to famine at different periods of gestation. Two additional samples of participants were recruited to act as control groups. These were 650 individuals born between November 1st 1943 and October 31st 1944 and 650 individuals born between 1st March 1946 and February 28th 1947. 27 people were excluded because their birth records were not available and 239 were excluded because they were born prematurely (gestational age below 259 days) which left 2414 live singletons.

The population registry of Amsterdam traced 2155 (89%) of the original 2414 eligible persons. Of these 265 had died and 199 had left the Netherlands and 164 refused to give their address to the researchers. This resulted in 1527 at the start of the study in 1995. Since then three rounds of data collection have been performed, in 1995-1997, in 2002-2004 and in 2008-2009. In 2012 1307 (54%) cohort members were alive, still living in the Netherlands with their address known to the researchers making them eligible for participation.

3.1.2.2 Exposure to famine

The famine period was defined according to official daily food rations for the general population aged 21 years and older which were set weekly by the authorities and varied according to class of labour. By November 1944, the official rations had fallen below 1000 calories per day and by April 1945, at the height of the famine, they were as low as 500 calories per day. Rations for children younger than one year never fell below 1000 calories and so they were relatively protected. The daily calories rose to more than 1000 calories after May 12 1945 and by June 1945 rations were more than 2000 calories per day. Prenatal exposure to undernutrition was defined as a daily maternal intake of less than 1000 calories during any 13 week period of gestation. This meant that those born between 7th January 1945 and 8th December 1945 were classified as exposed. Babies were considered to have been exposed to

undernutrition in late gestation if they were born between 7th January and 28th April 1945, mid gestation if they were born between 29th April and 18th August and early gestation if they were born between 19th August and 8th December 1945 (Figure 3.3).

This thesis uses data from the study that began in 2012 which, in accordance with previous publications, focuses on babies exposed to famine in early gestation. Previous research has found most effects on health (including mortality, coronary heart disease, diabetes, breast cancer and cognition) among this group (Roseboom et al., 2006). Also included are people born after 8th December 1945 who were conceived around the end of the famine and therefore exposed to famine in the preconception period. These groups are compared with a group of people born before 7th January 1945 (before the start of the famine) who were not exposed to famine during gestation.

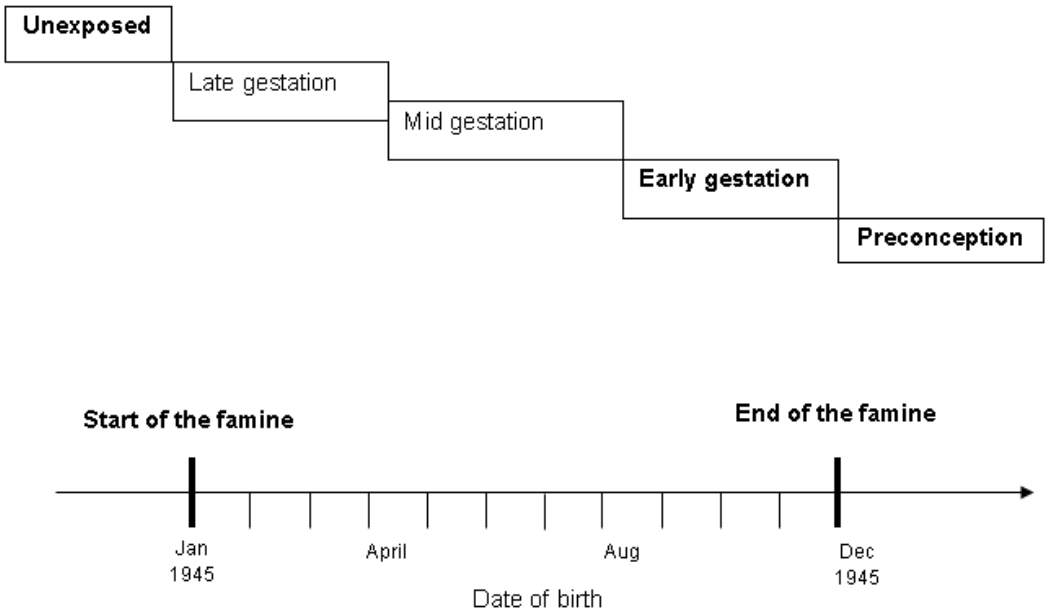


Figure 3.3: Diagram showing period of gestation in which members of the Dutch Famine Birth Cohort were exposed to the famine and corresponding month and year of birth.

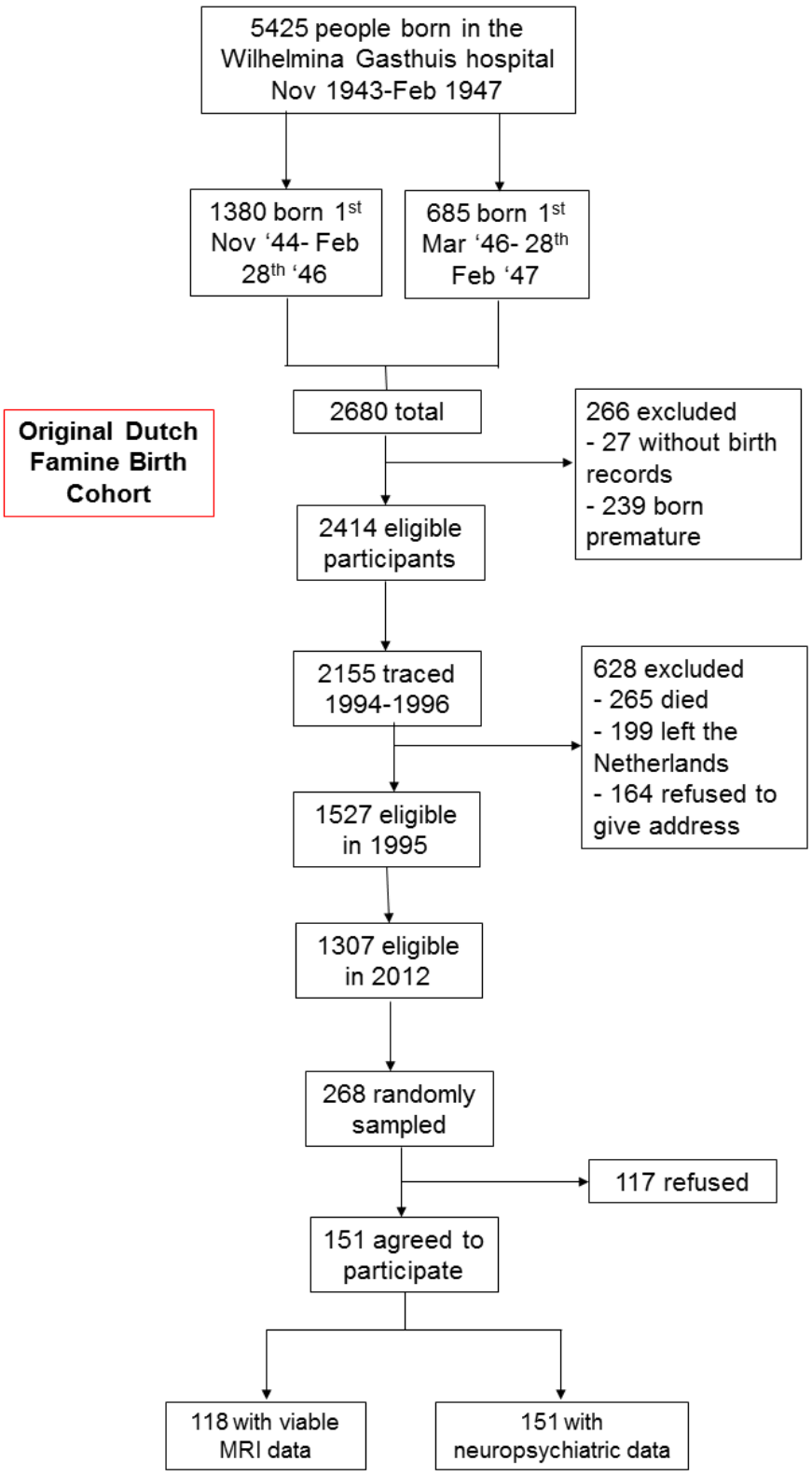


Figure 3.4: Flow chart of recruitment for the Dutch Famine Birth Cohort

2.1.1.3 Sample selection in this study

The study aimed to include a total of 150 participants: 50 of those born before the famine. 50 of those exposed to famine in early gestation and 50 of those conceived after the famine. Random equal samples were drawn out of the 268 eligible cohort members until there were 50 people in each group. All 150 participants provided demographic and neuropsychiatric data. 118 participants also completed MRI (Figure 3).

3.1.3 The Scottish Mental Surveys

The Scottish Mental Survey 1932 (SMS 1932) was designed by Scotland's Mental Survey Committee to investigate the mental ability of all children born in 1921 and attending school in Scotland on June 1st 1932. It was originally only meant to be conducted on a representative sample of children however it became a nation-wide survey after this proved difficult (The Scottish Council For Research in Education, 1933). In total 87,498 children completed a version of the Moray House Test No. 12 (MHT) intelligence test. The MHT consists of 71 items with a maximum score of 76. It was devised by Professor Godfrey Thomson and provides an estimate of a person's verbal reasoning ability. It is a well validated test of intelligence and has a correlation with the Stanford Binet IQ score of 0.80 (Deary et al., 2004) .

In 1947, after fears of a declining national intelligence the Scottish Mental Survey was repeated (SMS1947). The intention was to compare scores on the MHT No.12 between the two generations of age 11 school children. Therefore on Jun 4th 1947 70,805 age 11 children born in 1936 and attending school in Scotland sat the test. Despite earlier concerns the average score in the SMS 1947 was actually higher (36.7 out of 76) than the average score in the SMS 1932 (34.5 out of 76).

Ledgers containing the data from the SMS 1932 and the SMS 1947 were kept by the Scottish Council for Research and Education and were later discovered by a group of researchers which included Professor Lawrence Whalley and Professor Ian Deary. The discovery of these rich data led to two longitudinal cohort studies, the Lothian Birth cohort 1921 and the Lothian Birth cohort 1936 (Deary et al., 2004). These cohorts will now be described, starting with the youngest cohort, the Lothian Birth cohort 1936.

3.1.4 The Lothian Birth cohort 1936

The Lothian Birth cohort 1936 comprises 1091 surviving members of the SMS 1947. To date there have been four waves of testing; 2004-2007 (wave 1); 2007-2010 (wave 2); 2011-2014 (wave 3) and wave 4 is ongoing. The aim of the first wave of testing was to understand the genetic, physiological and psychosocial factors involved in aging using a series of questionnaires, cognitive and psychological assessments and blood and DNA samples. Wave 2 focused on mechanisms responsible for white matter damage and the effect on cognitive function and therefore repeated the assessments from wave 1 but also asked participants to complete a brain MRI scan. Subsequent waves have repeated these methods.

The data in this Thesis mainly come from the second wave of testing as this was the first to include brain imaging. This wave has a larger sample size and more complete imaging data than wave 3. However, Chapter 6 also includes sensitivity analyses to examine associations between early life factors and psychological measures at waves 1, 2 and 3.

3.1.4.1 Selection procedure

Recruitment for the LBC 1936 began in 2004. Between June 2004 and November 2006, researchers identified 3,810 people who lived in the Lothian area of Scotland (mainly Edinburgh city) and who were born in 1936 (and therefore may have participated in the SMS 1947), using the Community Health Index (CHI) and media advertisements. Invitations were sent out to 3686 people of which 1132 were interested and eligible to participate. A second invitation was then sent out to allow non-responders a chance to participate. 615 additional responses were received of which 94 were interested and eligible. Of these 1226 interested and eligible for the study, 85 participants withdrew before they were tested and 50 did not complete the assessments before the end of the testing in May 2007. This left a total of 1091 participants who entered the Lothian Birth Cohort study and completed the tests and questionnaires at wave 1 of testing (mean age=69.5, SD=0.8). An overview of this recruitment is presented in Figure 3.5.

Three years later, 866 participants returned for wave 2 of testing (mean age= 72.5, SD=0.7). 700 participants consented to having an MRI scan and 685 participants had some viable MRI data.

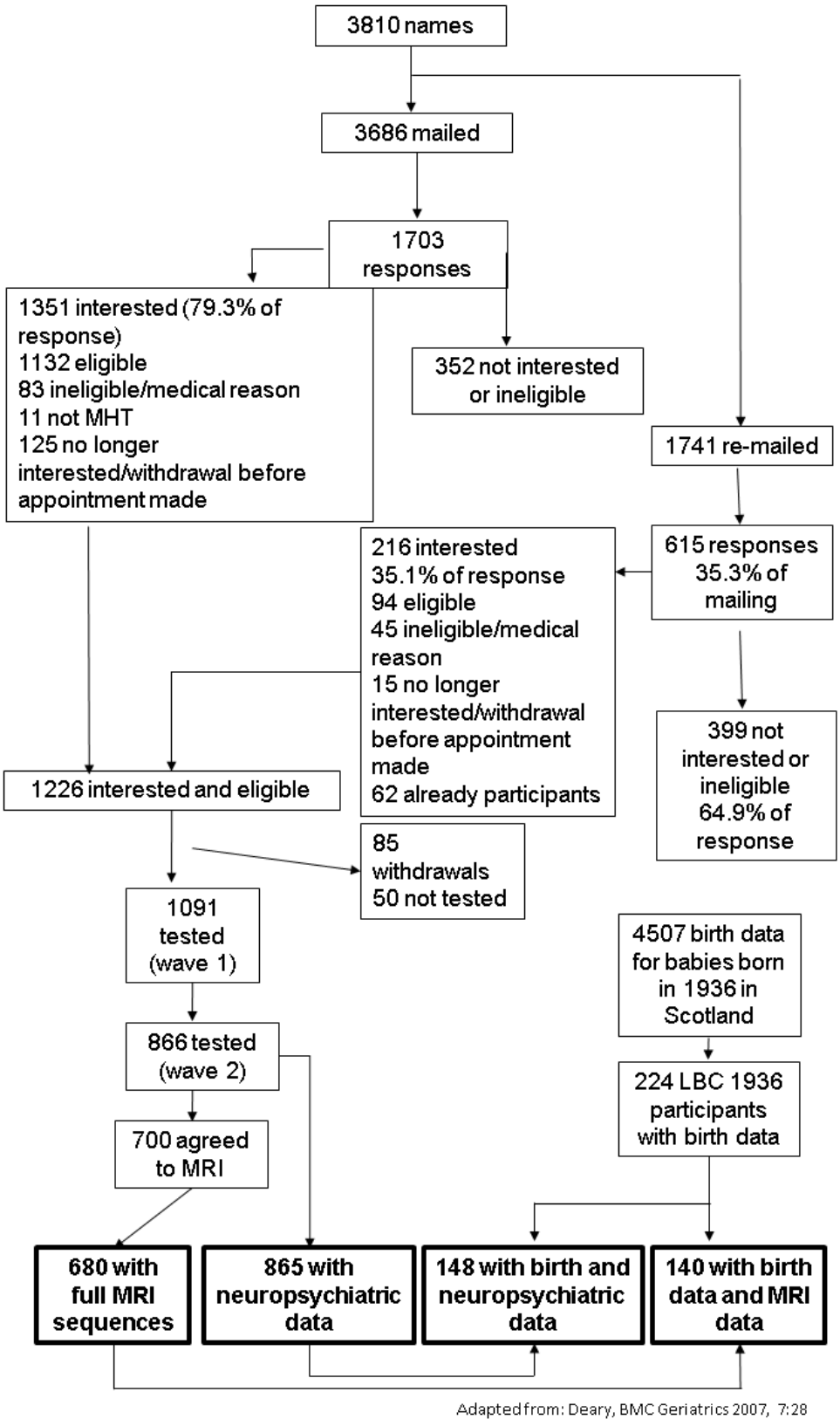


Figure 3.5: Flow chart of recruitment for wave 2 of LBC 1936

3.1.5 The Simpson Cohort

The Simpson cohort comprises of 130 people born in three Edinburgh Hospitals between 1921 and 1926. Initially the aim of the study was to recruit people who had been born in 1921 in the Royal Maternity and Simpson Memorial Hospital, who had participated in the SMS 1932, and who were living in the Lothian area in 2000. However researchers were unable to recruit enough participants born in 1921 and so recruitment was extended to include those born between 1922 and 1926.

3.1.5.1 Recruitment: 1921 born

People born in the Royal Maternity and Simpson Memorial Hospital in 1921 were identified using the Lothian CHI. People were initially invited to participate in the LBC 1921 which was a study which aimed to examine genetic influences on cognitive aging in healthy older adults by collecting social, cognitive, medical and genetic data. Participants were later asked if they wished to complete extra tests involved in the Simpson's study which included brain MRI, carotid Doppler scans, blood tests, apolipoprotein E genotyping, ankle branchial pressure index and additional questionnaires. In total 43 people born in the Royal Maternity and Simpson Memorial hospital in 1921 participated in the LBC 1921 and 28 of these agreed to also participate in the Simpson study. To try and increase the number of participants born in 1921 an additional 80 letters of invitation were sent to eligible people. Of these 80 people, 23 agreed, 32 refused, one person had died and 28 did not reply. A further 4 out of the initial 23 subsequently withdrew leaving 19 participants. Therefore there were 47 participants born in 1921; 28 LBC 1921 participants and 19 others. Of these, 43 completed cognitive and psychiatric assessments and 30 completed the MRI.

3.1.5.2 Recruitment: 1922-26 born

Recruitment was extended to include those born in Edinburgh hospitals between 1922 and 1926. Extensive advertising such as adverts in all local newspapers, posters in local hospitals, churches, community centres and GP surgeries and contacting charities resulted in recruitment of an additional 83 participants.

In total, 130 people born in Edinburgh hospitals took part in the Simpson's study, 115 agreed to MRI scans and 110 completed scans. This is detailed in Figure 3.6.

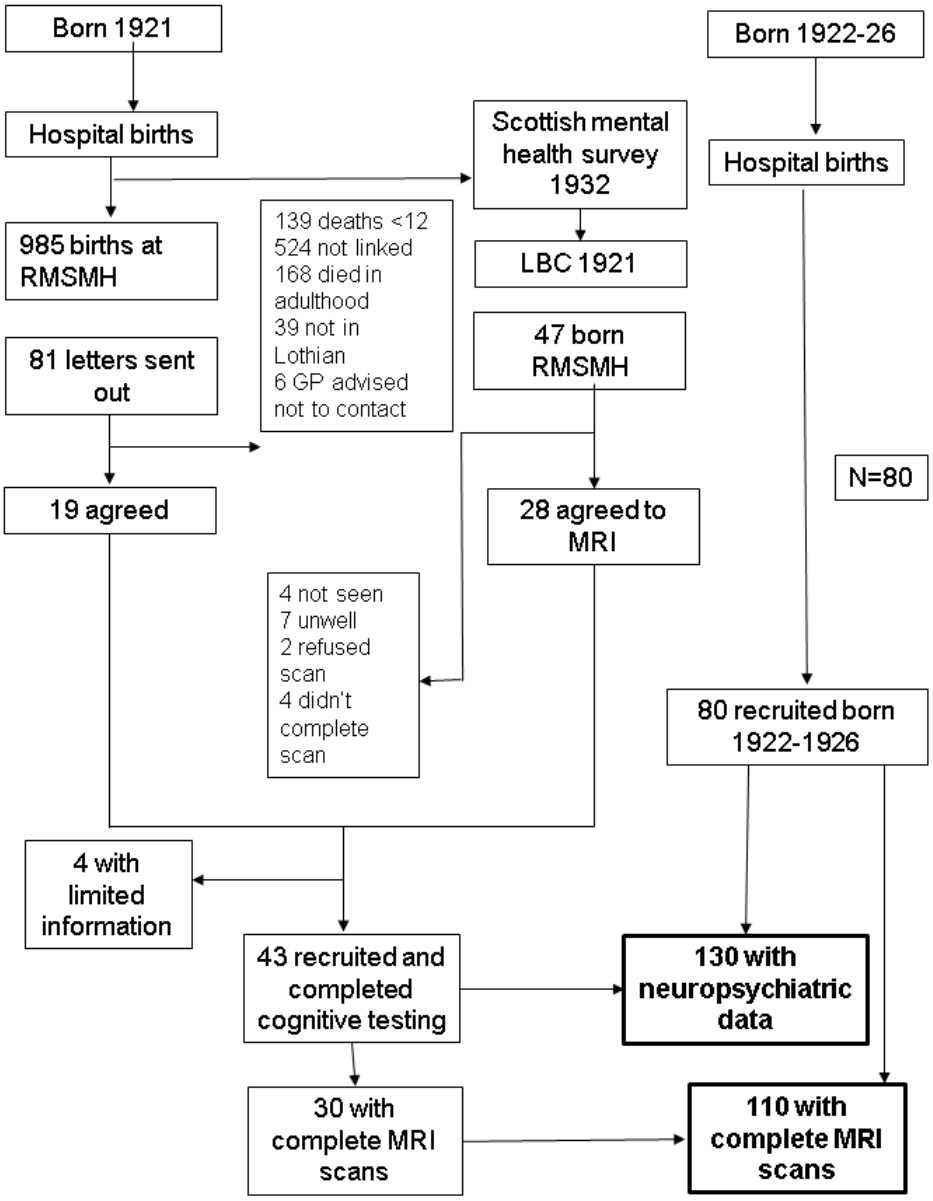


Figure 3.6: Flow chart of recruitment of the Simpson cohort

3.2 Study parameters

3.2.1 Birth factors

Perinatal and obstetric data varied between cohorts. Birth records were available for all participants in the Dutch Famine Birth Cohort and the Simpson cohort as they were all born in hospital and therefore had birth weight and other details recorded. Birth data for the STRADL study and LBC 1936 were only available for those born in hospital and is therefore limited.

For this Thesis all obstetric records for STRADL participants were taken from the ACONF database and linked to STRADL data using participants IDs. For the ACONF database birth records for each child were accessed after the school survey in the 1960s. They were taken from the Aberdeen Maternity and Neonatal Database (AMND) at the Aberdeen Maternity Hospital where the majority of cohort members were born. Birth data were available for all STRADL participants included in this Thesis.

Members of the Dutch Famine Birth cohort were born at the Wilhelmina Gasthuis Hospital in Amsterdam which kept detailed birth records which could be easily accessed by researchers at the start of the Dutch Famine Birth cohort studies.

Birth records for members of the LBC 1936 who were born in hospital were traced in 2011, by searching for a match with records from the Simpson Memorial Hospital, Bellshill Hospital, Lanarkshire, and Aberdeen Maternity Hospital: all the available birth records for Scotland for 1936. Birth records of all admissions to the Simpson Memorial Hospital in 1936 were obtained from the Lothian Health Services Archives in the University of Edinburgh's Main Library. Birth records were matched to each child's original birth certificate, which was accessed through the Scotland's People Centre in Edinburgh, using the parent's name, date of birth, occupation and home address. Of the 8249 registered births in Edinburgh in 1936 1816 were live singletons born at the RMSMH. Researchers were able to match birth records with birth certificates for 1589 individuals. Birth data was then matched to 1097 children's age 11 IQ score in the SMS 1947 using the child's full name and date of birth. Of these 1097 matches 224 were members of the LBC 1936 and at wave 2 140 had birth data and completed the MRI part of the study.

Members of the Simpson cohort were born at the Royal Maternity and Simpson Memorial Hospital, the Elsie Inglis Memorial Hospital and The Lying-in Institution. Birth records were kept from these hospitals and stored at the Special Collections at the Main Library, University of Edinburgh where they were obtained from at the start of the Simpson study.

Birth weight was measured in pounds and recorded to the nearest half a pound (STRADL), recorded in grams (Dutch Famine Birth cohort) or recorded in pounds and ounces and converted to grams (LBC 1936 and the Simpson cohort). Birth length was recorded in cm (Dutch Famine Birth Cohort, LBC 1936 and Simpson cohort). For this Thesis birth weight and length were used to calculated ponderal index (birth weight/(birth length)^3), a measurement of thinness. Gestational age was calculated using date of birth and date of the mother's last menstrual period. As the date of the last menstrual period was recorded as a month only, it was approximated at the 15th day of that month. Also collected from birth records was age (all cohorts) and marital status of the mother at the birth of the child (STRADL, Dutch Famine Birth cohort, Simpson cohort) and whether the participant was born pre term (<38 weeks) or full term (>38 weeks) (STRADL, Simpson cohort). In the Dutch Famine Birth cohort placental length was the longest placental diameter and width was the longest perpendicular diameter. Placental area was estimated as π×length×width×0.25. Head circumference was estimated as π×(biparietal diameter+occipitofrontal diameter) ×0.5. Mother's weight was that at the last prenatal visit, always within 2 weeks of birth measured in kilograms (Kg). In the Simpson cohort placental weight was measured in grams.

3.2.2 Childhood factors

Childhood and premorbid IQ

Childhood IQ was calculated by adjusting the raw scores from the Schonell and Adams Essential Intelligence Test (age 9 IQ, STRADL only) and Moray House Test number 12 (MHT) (age 11 IQ, LBC and Simpsons cohort only), for age in days at testing and placed on an IQ type scale (mean=100, SD=15).

Additionally premorbid IQ was estimated during the standardised interview using the Mill Hill Vocabulary scale (Raven and Court, 1993) (STRADL) and the National Adult Reading Test (NART) (Nelson and Willison, 1991) (the LBC 1936 and Simpson cohort). The Mill Hill tests requires participants to define 88 words arranged in

ascending difficulty. The NART requires participants to read aloud a list of 50 irregularly pronounced words. Both of these tests require recall of previously learnt information and are a measure of crystallised intelligence. Therefore they are both good measures of premorbid IQ. Scores on the Mill Hill Vocabulary scale and the NART correlate highly with IQ scores in adulthood and childhood, including the MHT and full scale IQ tests such as the Wechsler Adult Intelligence Scale (WAIS-IV) (Bright et al., 2016, Raven, 2000).

Education

Education was measured on a 10 point scale (Dutch famine study;1= Primary education not completed, 10=University completed) and by mean years (STRADL, LBC1936 and Simpsons study). To allow direct comparison of all cohorts in this Thesis, high and low education was calculated for each cohort. This corresponded to upper Secondary school and above vs Lower Secondary and above (Dutch famine) and >11 years vs ≤ 11 years (STRADL, LBC1936, Simpsons study). Data on educational attainment was collected for STRADL and the LBC 1936 (no qualifications, O-level, A-level, semi-professional, or degree). This was dichotomised into no qualifications vs O level and above for this Thesis.

Childhood SES

In this thesis the main indicator of childhood SES is parental occupation which was collected in all cohorts. To allow direct comparison across all cohorts low and high childhood SES were classified as manual and non-manual occupation at time of the child's birth (STRADL, Dutch Famine Birth cohort) or at age 11 (LBC 1936 and Simpson cohort). This data was obtained from birth records (STRADL, Dutch Famine cohort), the General Register Office's Census, 1951 Classification of Occupations (LBC1936) and self-reported by participant at the time of the interviews (LBC 1936 and Simpsons cohort). Proxy measures of childhood SES were also collected in the LBC1936 and Simpson cohort during the interview. These included number of years of education that the Father completed (LBC 1936 only), number of people living in their home, number of rooms and toilets, number of people sharing a toilet and whether their toilet was indoor or outdoor. Overcrowding index was calculated by dividing the number of people living in the home by the number of rooms in the home.

A subsample of STRADL participants have some additional socioeconomic data regarding housing conditions and social background of the parents (e.g. number of

people in the household, number of rooms, number of years of education of the parents) which was collected as part of the ACDS. However this was only collected for a random sample of 1 in 5 children (2510 participants). The number of participants in STRADL with this additional information is too low to be included in the analyses in this thesis.

3.2.3 Adult factors

Demographic details, self-reported medical history, employment history and psychometric assessment were obtained during standardised interview in 2015-2017 (STRADL), 2012 (Dutch Famine Birth Cohort), 2007-2010 (LBC 1936) and 2000 (Simpson cohort).

Participants from the Dutch Famine Birth Cohort were visited at home and interviewed by a trained researcher. Participants from STRADL, the LBC 1936 and Simpson cohort were interviewed and tested individually by a trained researchers at the Aberdeen Biomedical Imaging Centre (STRADL) and the Welcome Trust Clinical Research Facility (WTCRF) Western General Hospital, Edinburgh (LBC 1936 and Simpson cohort). Seven participants from the Simpson cohort were interviewed at their home.

Hospital Anxiety and Depression Scale (HADS)

In the Dutch Famine cohort, the LBC 1936 and the Simpson cohort mood during the past 7 days was assessed using the Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983) (HADS). This is a self-report questionnaire comprising of two subscales: HADS-anxiety scale (HADS-A) and HADS-depression scale (HADS-D). Each subscale has seven items with a maximum score of 21, with a higher score indicating higher anxiety or depressive symptoms. This thesis examines individual scores for each component. This scale was originally developed for use in hospital patients but has since been validated in community settings. Scoring the HADS as two subscales of anxiety and depression has been deemed appropriate (Bocéréan and Dupret, 2014).

HADS data are available for all participants: 151, 1091 and 130 participants in the Dutch Famine Birth Cohort, the LBC 1936 and the Simpson cohort respectively. HADS-A scores were available for all 280 STRADL participants.

The Quick Inventory of Depressive Symptomology (QIDS)

Symptoms of depression in STRADL were measured using The Quick Inventory of Depressive Symptomology (QIDS) (Rush et al.), a 16 item scale adapted from the longer 30-item Inventory of Depressive Symptomology (IDS). The QIDS measures overall severity of depressive symptoms by addressing each of the nine DSM-IV symptom domains for major depressive disorder. The scale has a maximum score of 27 with each item scored 0-3. The scale contains four items which examine sleep disturbance, four items which examine changes in appetite or weight, and two items which examine psychomotor disturbance. For each of these three domains the highest rating item is used and is added to the score of the remaining six domains which are assessed using one item only; sad mood, concentration, self-criticism, suicidal ideation, interest and energy/fatigue.

Health covariates

Medical history was a self-reported in all cohorts during the interviews. Participants were asked If a doctor had ever told them that they had hypertension or high blood pressure, diabetes, a stroke or "mini stroke" (transient ischaemic attack- TIA) or any other significant illness. Participants were also asked if they were an ex, current or never smoker, how many cigarettes they smoked a day and at what age did they start and stop smoking.

Current cognition was measured using the Raven's Progressive Matrices (Raven and Court, 1993) (STRADL), the Alice Heim 4 test (Heim, 1955) (AH4) and the Mini Mental State Exam (MMSE) (Folstein et al., 1975) (LBC 1936, Simpson cohort).

Adult SES was based on the highest of either the participant's or their partner's occupation which was self-reported and defined according to The Registrar-General's Social Classes (1991) (STRADL), the International Index of Occupational Status-92 (Dutch Famine), the Office of Population Censuses and Survey's Classification of Occupations, 1980 (LBC 1936) and the Registrar General's Classification, obtained from the 1951 Census Classification of Occupations (Simpson cohort. For this thesis occupation was divided into manual or non-manual for all cohorts.

3.2.4 Brain MRI acquisition protocols

This Thesis used a combined approach of qualitative visual rating scales and computational image processing methods. In some cases (WMHs and brain atrophy), the same metric is measured and so qualitative and quantitative methods are

complementary. Some imaging variables were obtained specifically for this thesis whilst others were obtained at the time of the initial testing. These will be described in the relevant sections.

Brain imaging acquisition for the Dutch Famine birth cohort (de Rooij et al., 2016), the LBC 1936 (Wardlaw et al., 2011) and the Simpson cohort (Shenkin et al., 2005) have been described previously in detail, including description of additional imaging such as diffusion-tensor imaging (DTI) and carotid Doppler ultrasound. However this section will give an overview of the methods used for this Thesis only.

Participants were scanned on a Philips Achieva 3.0T TX (STRADL), a 3T Philips Ingenia, Best, the Netherlands scanner with a 16-channel DStream Head-Spin coil (Dutch Famine cohort), a 1.5T GE Signa HDx scanner operating in research mode (LBC1936, Simpson cohort). The small vessel disease (cSVD) components and brain volumes were ascertained from axial fluid-attenuated inversion recovery (FLAIR), T1, T2, T2* weighted sequences. Sequence parameters for all cohorts are shown in Table 3.2.

Table 3.2: Sequence parameters for MRI scanning in all cohorts

Sequence name	Acquisition method	Field of view (mm)	Matrix	Slices	Thickness (mm)	Voxel (mm)	TR/TE/TI (ms)
STRADL							
T2-weighted	3D TSE	250	512 x 512	320	0.5	0.5	2500/314
SWI	FFE	230	768 x 768	130	1	0.3	31/7.2,14.4,20.6,26.8
FLAIR	3D IR FSE	240	256 x 256	160	1	0.94	8000/349/2400
T1-weighted volume	3D IR TFE	240	256	160	1	0.94	8.3/3.8/1031
Dutch Famine Birth cohort							
T2-weighted	2D TSE	230 x 230	512 x 512	28	4	0.45 x 0.45	3000/80
SWI-weighted	3D SWI	220 x 220	448 x 448	220	1.2	0.49 x 0.49 x 0.6	19.8/25.7
FLAIR	3D	250 x 250	240 x 240	321	1.1	1.1 x 1.1 x 1.12	4800/365
T1-weighted volume	3D TFE	256 x 256	256 x 256	180	1.0	1.1 x 1.1 x 1.2	6.8/3.1
LBC 1936							
T2-weighted	FSE	256 x 256	256 x 256	80	2	1 x 1 x 2	1 1320/105
T2*-weighted	Gradient echo	256 x 256	256 x 192*	80	2	1 x 1 x 2	940/15
FLAIR	FSE	256 x 256	256 x 192*	40	4	1 x 1 x 4	9002/147/2200
T-1 weighted mapping	FSPGR	256 x 256	128 x 128*	72	2	1 x 1 x 2	6/2
T1-weighted volume	3D IR-Prep FSPGR	256 x 256	192 x 192*	160	1.3	1 x 1 x 1.3	10/4/500
Simpson cohort							
T2-weighted	FSE	240 x 240	256 x 256	-	5	-	6300/102
T2*-weighted	Gradient echo	-	-	-	-	-	-
FLAIR	FSE	240 x 240	256 x 192	-	5	-	9000/140/2200
T-1 weighted mapping	FSPGR	240 x 240	256 x 224	-	5	-	450/8
T1-weighted volume	3D IR-Prep FSPGR	240 x 240	256 x 256	-	1.7	-	400

* Zero filled to 256 x 256; TR: repetition time; TE: echo time; FLAIR: Fluid-attenuated inversion recovery; SWI: susceptibility weighted imaging; IR-Prep: inversion recovery prepared; FSPGR: fast spoiled gradient echo; FSE: fast spin echo. – is used where data were not available.

3.2.4.1 Qualitative image analysis

This section will outline the qualitative image analysis which was conducted in all cohorts. For STRADL and the Dutch Famine Birth cohort qualitative image analysis was conducted specifically for this Thesis by one researcher (Ellen Backhouse). For the LBC 1936 qualitative analysis was conducted around the time of the initial data collection by several trained researchers.

All images were independently rated for presence of WMHs, lacunes, cerebral microbleeds and enlarged perivascular spaces (EPVS). A 4-point composite scale was then composed which assigned one point for each of these MRI markers of cSVD. Markers of cSVD were assessed using previously defined rating criteria, (Cordonnier et al., 2009, Potter et al., 2015, Wardlaw et al., 2011), converted to dichotomous point scores and summed to create the cSVD score, with a minimum score of 0 and a maximum score of 4 (Staals et al., 2014, Huijts et al., 2013, Klarenbeek et al., 2013).

Also assessed during qualitative analysis was severity of superficial and deep atrophy (Farrell et al., 2009) and presence of cortical or subcortical infarcts. Further details of this scoring for each marker is given in the next section. The scoring sheet used to document each of these MRI markers is given in appendix 3A.

All MRIs were assessed by either a trained researcher (Ellen Backhouse, STRADL, Dutch famine study; Carly Rivers, Simpson study), or a certified and registered neuroradiologist (Professor Alison Murray, STRADL; Zoe Morris, LBC1936; Professor Joanna Wardlaw, Dutch famine study, LBC 1936, Simpson study) blind to all other data. A proportion of scans in some studies were checked to ensure consistency. Interrater kappa statistics for WMH, EPVS and micro-bleeds were 0.85, 0.88-1.0 and 0.82 in the Dutch famine cohort. In LBC 1936 intraclass correlation coefficient for WMH was 0.96 and intra and interrater kappa statistics for EPVS were 0.8-0.9 (Aribisala et al., 2014).

3.2.4.2 Components of the cSVD scale

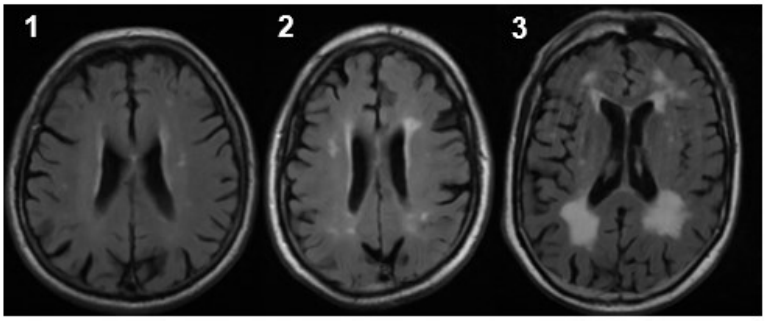
White matter hyperintensities

White matter hyperintensities (WMH) were defined as punctuate, focal or diffuse lesions in the deep or periventricular white matter, basal ganglia or brainstem, visible as areas of hyperintensity on FLAIR images in respect to normal appearing white or grey matter.

Severity of WMHs were graded according to the Fazekas scale (Fazekas et al., 1987) which distinguishes periventricular WMHs and deep WMHs and grades them from 0 (absent) to 3 (severe). A score of 1 is defined as caps or pencil thin lining (periventricular WMH Figure 3.7 A1) or punctuate foci (deep WMH, Figure 3.7 B1); a score of 2 is defined as a smooth halo (periventricular WMH, Figure 3.7 A2) or beginning to confluence (deep WMH, Figure 3.7 B2) and a score of 3 is defined as irregular periventricular signal extending into the deep white matter (periventricular WMH, Figure 3.7 A3) or large confluent areas (deep WMH, Figure 3.7 B3).

For the cSVD scale one point is awarded for the presence of moderate or severe WMHs, defined as periventricular hyperintensities with a score of 3 on the Fazekas scale and/or deep white matter with a score of 2-3 on the Fazekas scale.

A. Periventricular lesions



B. Deep white matter lesions

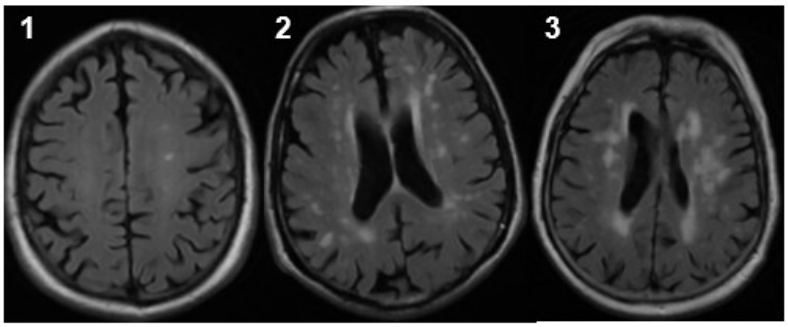


Figure 3.7: Axial FLAIR images showing examples of the grading of white matter hyperintensities using the Fazekas scale. Examples are presented for scores 1-3 for (A) periventricular white matter hyperintensities (B) deep white matter hyperintensities.

Lacunes

Lacunes were defined according to international consensus definition (Wardlaw et al., 2013) as oval or round CSF cavities with a diameter of 3-15 mm, in the deep white or grey matter (Figure 3.8).

For the cSVD scale one point was given if one or more lacune was identified on T2-weighted or FLAIR imaging.

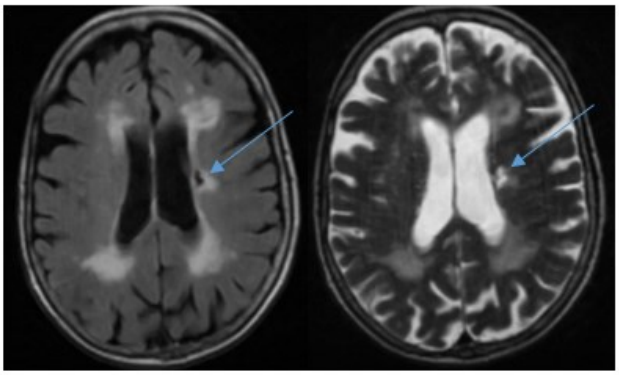


Figure 3.8: Axial (A) FLAIR and (B) T2-weighted MRI showing a lacune in a participant from the LBC 1936.

Cerebral microbleeds

Cerebral microbleeds were defined according to international consensus definition (Wardlaw et al., 2013) as round hypointense lesions found in the basal ganglia, brain stem, cerebellum (deep microbleeds) or at the cortico-subcortical junction (lobar microbleeds), with a diameter <10 mm that were not attributable to flow voids in small vessels. Number and location of microbleeds were coded using a simplified version of the Brain Observer MicroBleed Scale (BOMBS) (Cordonnier et al., 2009). Microbleeds were identified on susceptibility weighted images (SWI) in (STRADL and the Dutch Famine Birth cohort) or on T2*-weighted gradient echo-images (the LBC 1936 and Simpson cohort) (Figure 3.9).

For the cSVD scale one point was given for presence of one or more cerebral microbleed (deep or lobar).

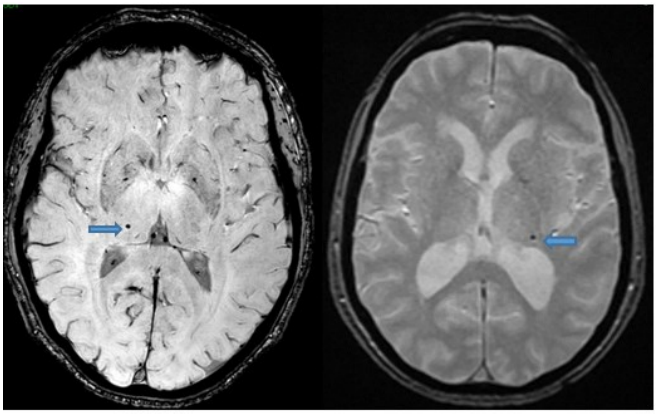


Figure 3.9: Axial (A) SWI and (B) T2* weighted MRI showing a cerebral microbleed in the basal ganglia of two participants from STRADL and LBC 1936.

Enlarged perivascular spaces

Enlarged perivascular spaces were defined as small punctuate or linear hyperintensities <3mm in the basal ganglia or centrum semiovale. Severity of EPVS were scored according to a semi quantitative validated scale (Doubal et al., 2010) which grades from 0 to 4 according to the total number of EPVS visible each hemisphere and overall. Grade 0 is defined as no EPVS; grade 1 as <10 EPVS; grade 2 as 11-20 EPVS; grade 3 as 21-40 EPVS and grade 4 as >40 EPVS. The images presented in figure 3.10 are examples of single slices derived from complete scans of four different STRADL participants showing EPVS grades 1-4 in the basal ganglia

For the cSVD scale one point is awarded for the presence of moderate or severe EPVS identified on T2-weighted imaging in the basal ganglia, defined as a score of 2-3 on the semi-quantitative scale.

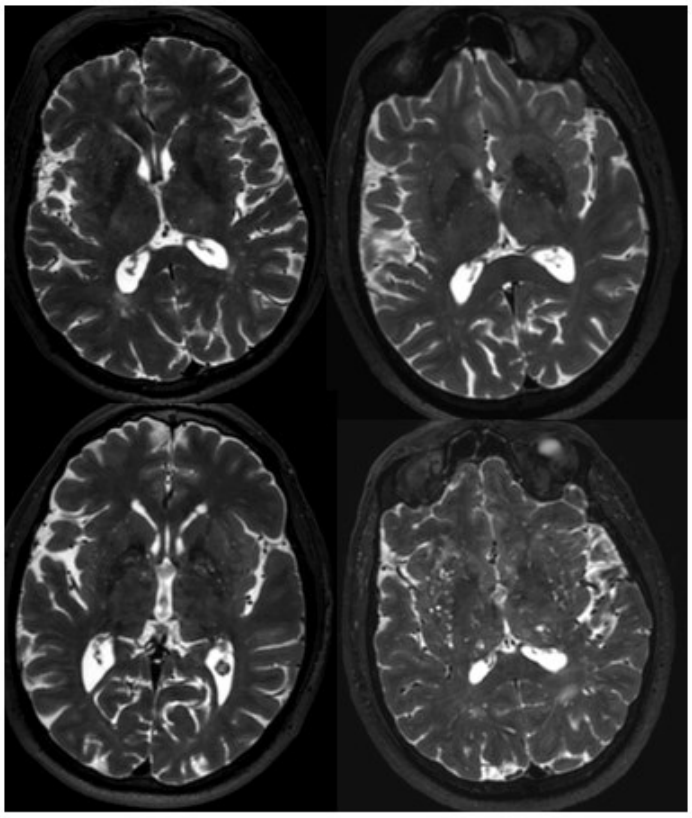


Figure 3.10: Axial T2-weighted MRI showing punctuate perivascular spaces in the basal ganglia (from left to right) grade 1, grade 2, grade 3 and grade 4. Examples are taken from MRI scans of STRADL participants.

Additional variables

Infarcts

Symptomatic and asymptomatic infarcts were coded for size and location based on vascular territory using a validated stroke lesion rating scale (Wardlaw and Sellar, 1994) which differentiates infarcts into cortical, lacunar, borderzone and brainstem/cerebellar. Old haemorrhages were also coded by size and location (Wardlaw 1994) and lacunar infarcts were coded as having cavitated or not.

Cerebral atrophy

Cerebral atrophy was scored on a 6 point scale according to a validated normative age template (Farrell et al., 2009). Deep (enlargement of the ventricles) and superficial (enlargement of the sulci) components were rated separately and summed to give a total score of 2-12 (Figure 3.11).

Atrophy was dichotomised into moderate or severe, defined as a score of 7 and above and mild, defined as a score of less than 7.

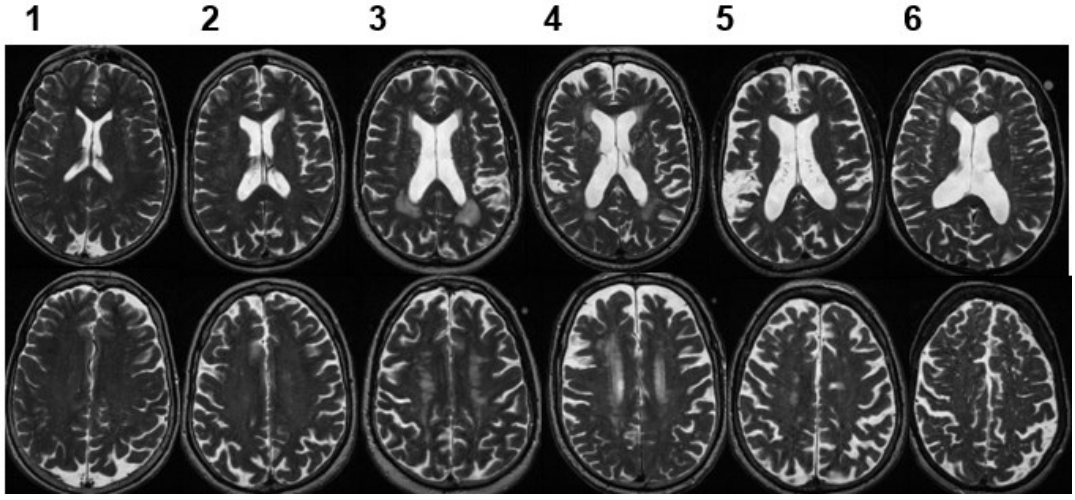


Figure 3.11: Axial T2-weighted MRI showing deep (top) and superficial (bottom) atrophy scored 1-6 based on a validated normative age template (Farrell et al., 2009). All are images of participants in the LBC 1936.

3.2.4.2 Structural image analysis

This section will outline the volumetric measurements obtained from T1, T2, T2* and FLAIR weighted structural MRI sequences in the LBC 1936 and Simpson cohort. These data are not currently available for STRADL and are available but have been published previously for the Dutch Famine Birth cohort (de Rooij et al., 2016). A general overview will be given for each cohort and then further details will be given for each specific brain region.

In the LBC 1936 whole brain volume, WMH volume intracranial volume (ICV) and volumes of the ventricles, grey matter, normal appearing white matter, hippocampi and cerebral spinal fluid were measured. All structural analysis, including generation of semiautomatic tissue masks and manual editing, was completed by various trained researchers at the end of each wave of data collection (waves 2-4). In accordance with the qualitative imaging, this thesis will include the total and regional brain volumes obtained from participants at wave 2.

In the Simpson cohort whole brain volume and brain sub regions (frontal and temporal lobe, amygdalo hippocampal complex and corpus collosum) were measured. The majority of the structural image analysis which will be used in this Thesis was conducted at the end of data collection and analysed by a trained researcher (Carly Rivers). However as WMH volume and ICV were not originally obtained for the Simpson cohort, semiautomatic ICV and WMH masks were generated by a trained Research Fellow (Dr Michael Stringer) and manually edited by a trained researcher (Ellen Backhouse) for this Thesis. This maximised the data available and allowed direct comparison of cohorts.

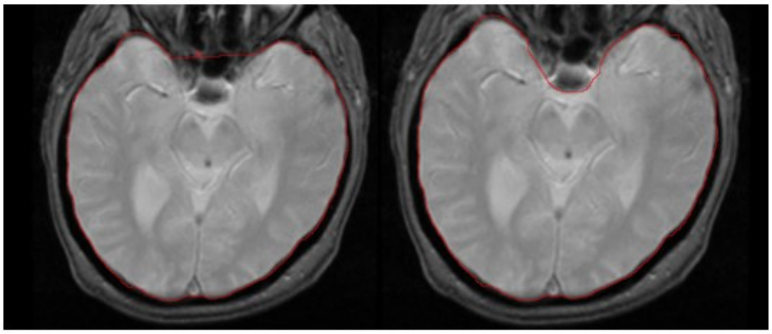
In both cohorts each sequence was converted from DICOM to either Analyze 7.5 or NIFTI-1 format. T1W, T2*W and FLAIR scans are registered to T2W scans using a FSL-FLIRT, a registration tool freely available from the FMRIB software library (Jenkinson et al 2002). All analysis were performed using Analyze^{TM} software (AnalyzeDirect, Stillwell, KS, USA).

Intracranial volume

In the LBC 1936 and the Simpson cohort the intracranial volume (ICV) was obtained semi automatically from T2* weighted sequences using the Object Extraction tool in Analyze 9.0 (LBC 1936) and Analyze 12.0 (Simpson cohort). The ICV included the

contents within the inner skull table. The inferior boundary of the ICV was the slice superior to the tip of the odontoid peg at the foramen magnum. Any tissue erroneously included inferior to this slice was deleted during manual editing of the mask along with the pituitary gland, the carotid arteries, veins and the jugular bulb (Figure 3.12). However the sigmoid and transverse sinuses were included. Manual editing of the ICV masks was done using Analyze 9.0 or Mango software and ICV calculated mm^3 using MATLAB.

A.



B.

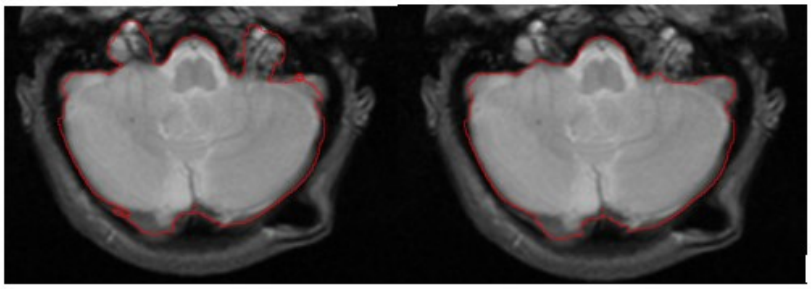


Figure 3.12: ICV mask before (left) and after (right) the removal of the (A) the pituitary gland and (B) the jugular bulb and carotid artery

White matter hyperintensities

All tissue segmentation In the LBC 1936 and segmentation of WMHs in the Simpson cohort, were processed using the semiautomatic segmentation tool MCMxxxVI which fuses two MRI sequences in red-green colour space to enhance visual differences

between tissues and allow specific features of interest to be extracted. It is described in detail in (Valdés Hernández et al., 2010). MCMxxxVI uses a statistical-based method Minimum Variance Quantization to separate each type of tissue and to represent images in a reduced number of clusters mapped in the same colour space (Valdés Hernández et al., 2010). The resulting tissue masks were stored in Analyze or NIFTI format and all segmented images were visually inspected and manually edited for any incorrectly classified tissues, resulting in volumes for each structure in mm^3.

WMH volume was calculated using binary masks generated in MATLAB. WMH masks were obtained by fusing T2* weighted and FLAIR images in red and green respectively, in Analyze 9.0 or 12.0. The resulting fused red-green image was then loaded into MATLAB where the intensity of the image was adjusted to identify the specified tissue and a binary WMH mask was generated using MCMxxVI. WMH masks were manually edited on FLAIR images using Analyze 9.0 or Mango 4.0 (Research Imaging Institute UTHSCSA). Any misidentified WMHs after the superior limit of the white matter were removed and each slice was checked for artefacts (Figure 3.13) according to a brain imaging processing manual. WMH volumes were generated in mm^3 using MATLAB.

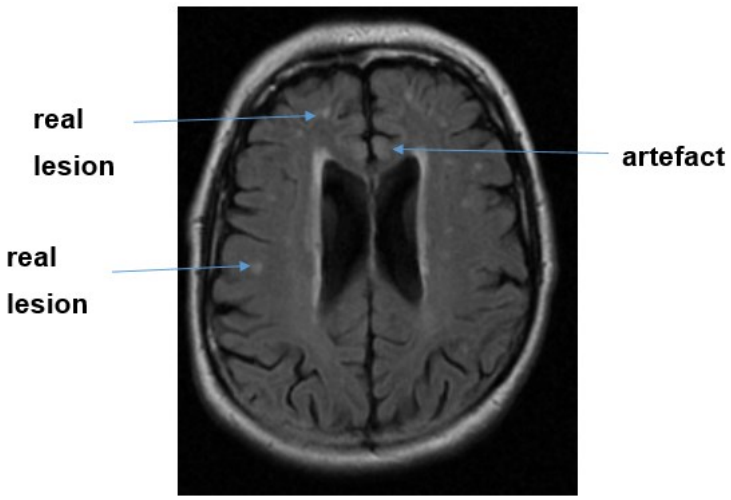


Figure 3.13: Axial FLAIR image showing real punctuate lesions in the deep white matter and artefacts in the CSF/tissue interface.

Whole brain volume

In the LBC 1936 whole brain volume was derived by subtracting the CSF mask from the ICV masks previously generated using the image calculator in Analyze 9.0. This resulted in a mask that only contained brain tissue and so was used as a measure of whole brain volume.

In the Simpson cohort brain volumes were measured from the 3 directional 128-slice scan at 90º to hippocampus. The brain was thresholded to eliminate the maximum of 'non-brain' tissue (bone, meninges) before performing the analysis. The whole brain volume includes all brain tissue, with a limit imposed in a horizontal line across the bottom-most part of cerebellum as posterior limit.

In both cohorts a measure of global brain atrophy was constructed by dividing the whole brain volume by the ICV and multiplying by 100.

Lothian Birth Cohort 1936 only

Cerebrospinal fluid and normal appearing white matter

CSF and normal appearing white matter volumes were calculated using a similar method to WMHs. T1 and T2 weighted images were fused using Analyze 9.0 to produce a red-green image and a binary CSF and normal appearing white matter mask were generated in MATLAB using MCMxxxVI. These masks were checked and erroneously identified tissue was manually removed. CSF and normal appearing white matter volumes were calculated in mm^3 using MATLAB.

Grey matter volume

Deep and cortical grey matter volume was extracted by subtracting the CSF, NAWM and WMH masks from the ICV mask previously generated. These were also visually inspected and manually edited if necessary and volumes were calculated in mm^3.

Hippocampal volume

Right and left hippocampal volume masks were generated using FSL's FIRST automated segmentation software (Patenaude et al., 2011) on T1-weighted images. Noise reduction was applied to the T1W volume which were then registered using FSL's FLIRT to an age-appropriate registration template (Farrell et al., 2009). The masks were then visually assessed for accuracy and manually edited using Analyze 9.0.

Simpson cohort

Corpus callosum area

Corpus callosum area was derived by manually traced around the edges of the corpus callosum on sagittal T1-weighted images (Figure 3.14).

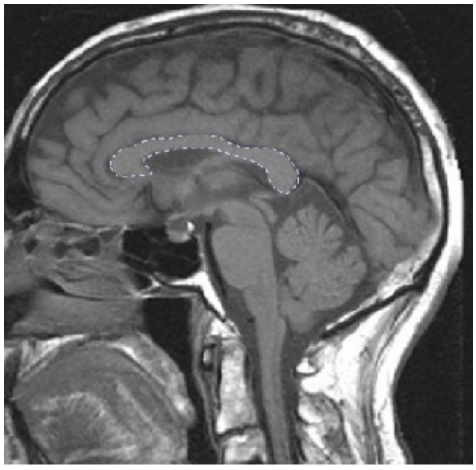


Figure 3.14 Definition of corpus callosum

Ventricular volume

The volume of the lateral, 3 rd. and 4th ventricles were obtained from coronal MRI.

Frontal lobe volume

Frontal lobe volumes were measured from the slice in which the frontal pole could be distinguished from the meninges. Measurements were made using automated methods with manual tracing to separate the lobes through the inter-hemispheric fissure. Frontal lobes were split into left and right hemispheres and included from the pole of the frontal lobes to the slice immediately preceding the genu of the corpus callosum (where the corpus callosum is fully formed) (Figure 3.15).

Temporal lobe volume

Left and right temporal lobes were measured separately including tissue from the temporal poles to the last slice in which the fibres of the crux of the fornix appears distinct from the hippocampus and the walls of the lateral ventricles (Figure 3.16).

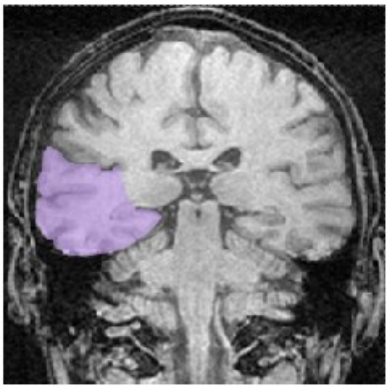


Figure 3.15: Definition of the temporal lobe

Amygdalo-hippocampal complex (AHC)

This was defined as subiculum, hippocampus proper and dentate gyrus with the alveus and fimbria. The AHC was measured bilaterally using manual tracing from the first slice where the temporal stem is fully formed until the last slice of temporal lobes, where the crus fornicis appeared distinctly.

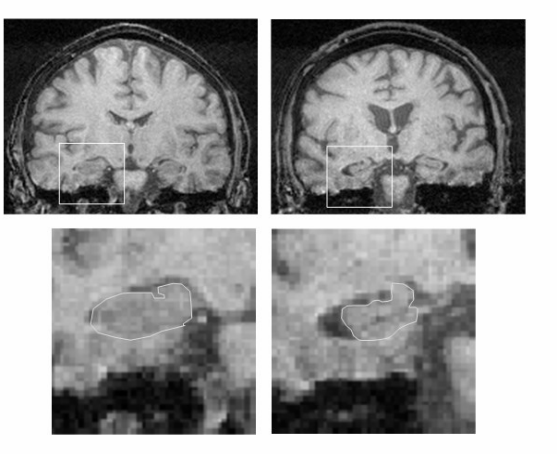


Figure 3.16: Definition of the amygdalo hippocampal complex

Summary

This chapter has described the recruitment procedures of STRADL, the Dutch Famine Birth cohort, the LBC 1936 and the Simpson cohort. It has also given an overview of the main study parameters which will be examined in the next three chapters of this Thesis; the early life factors; the neuropsychiatric data and MR imaging variables. Details of the statistical analysis will be given in each chapter.

4. Cerebrovascular disease and depressive symptoms in later life.

4.1 Introduction

Depression and depressive symptoms are frequently encountered in older individuals. In community based studies estimated prevalence of major depressive disorder (MDD) varies between 1.6% and 5.4% in those over the age of 60 (Park et al., 2015, Sjöberg et al., 2017). Among those who develop clinical depression in later life up to 50% will experience additional episodes (Trivedi et al., 2006, Hardeveld et al., 2010). Furthermore, approximately one third of people are treatment resistant and do not respond to antidepressants or therapy (Trivedi et al., 2006, Paroni et al., 2017). Even in the absence of a clinical diagnosis of MDD, depressive symptoms are associated with high rates of morbidity (Meeks et al., 2011).

Depression in younger adults is associated with family history of depression (Kendler et al., 2009) and a higher prevalence of personality disorder or personality traits such as neuroticism (Gade et al., 2015) . In contrast, depression in later life is associated with cerebrovascular comorbidities. Studies have shown higher burden of white matter hyperintensities (WMH) (van Agtmaal et al., 2017), worse white matter integrity (Wen et al., 2014, Pasi et al., 2016) and more lacunes, micro-bleeds and silent brain infarcts (van Agtmaal et al., 2017) in elderly depressed patients compared to aged matched controls. Furthermore, late-life depression has been associated with reductions in total brain volume, grey matter volume and changes in the frontal-subcortical and limbic regions (Sexton et al., 2013b, Du et al., 2014, Tudorascu et al., 2014).

Comorbid anxiety disorders have been estimated to affect up to 38.6% of adults over the age of 60 with depression (van der Veen et al., 2014). Less research has been conducted on late life anxiety, however it is also common affecting around 3-14% of older adults (Vasiliadis et al., 2013) and an additional 15-20% of people experience symptoms of anxiety that do not meet criteria for diagnosis (Wetherell et al., 2005). Diagnosis of psychological conditions such as anxiety and depression can be challenging, particularly in older people. Depression and anxiety commonly occur alongside other medical conditions, both physical and psychological which can cause difficulties in distinguishing between psychological and physical symptoms as

physical co-morbidities can restrict the ability to engage in activities (Bryant et al., 2009).

The presence of depression and anxiety is associated with cognitive impairment (Beaudreau and O'Hara, 2008, Barnes et al., 2012) and poorer quality of life (Chachamovich et al., 2008). Establishing a clear link between cSVD and symptoms of anxiety and depression may lead to a better understanding of the causes of these illnesses. It may also lead to more effective treatment which would benefit those who are treatment resistant. This is especially important given the high personal and societal cost of psychiatric illness in the older population (Prince et al., 2015).

Studies examining cerebral small vessel disease (cSVD) and depression in later life have mainly focused on the role of WMHs. However some studies suggest that markers other than WMHs, such as lacunar infarcts and cerebral microbleeds, may be associated with increased depressive symptoms (van Agtmaal et al., 2017, Grool et al., 2011). However other studies have reported no association (van Sloten et al., 2015, Pasi et al., 2016). No previous studies have examined total cSVD burden and there are few studies which have investigated cSVD and symptoms of anxiety in older adults. Therefore the first aim of this study was to examine the relationship between total and individual markers of cSVD and a) depressive symptoms on the depression subscale of the HADS (HADS-D) and b) symptoms of anxiety on the anxiety subscale of the HADS (HADS-A).

The second aim of this study was to examine total and regional brain volumes and a) depressive symptoms on the HADS-D b) symptoms of anxiety on the HADS-A. The hypothesis was that total and individual markers of cSVD would be associated with increased scores on the HADS-D and A.

4.2 Methods

Methods for recruitment and neuroimaging are presented in detail in Chapter 3.

4.2.1 Participants

STRADL

This chapter uses data from 253 STRADL participants with MRI, demographic and neuropsychiatric data.

The Dutch Famine Birth cohort

The current study included a total 151 cohort members. For the MRI part of the study 33 people withdrew due to anxiety of the scanner (n=8), metal in the body (n=15) and not wanting to visit the hospital (n=9). Data were lost for one participant making a total of 118 participants with viable MRI data. Demographic and neuropsychiatric data were available for all participants. In accordance with previous publications in some analyses, this study compared participants who were exposed to famine in early gestation (n=41) with two non-exposed groups; those born before the famine (n=35) and those conceived after the famine (n=42).

The Lothian Birth cohort 1936

At wave 2, 700 participants provided some usable MRI sequences (fifteen were removed for missing sequences). 680 participants had complete MRI sequences and a further 5 had some usable sequences. Demographic and neuropsychiatric data were available for all participants.

The Simpson Cohort

The chapter uses data from 110 members of the Simpson cohort with MRI, demographic and neuropsychiatric data.

4.2.2 MRI analysis

Details of the methods used to assess cSVD burden and brain volumes are given in Chapter 3. Briefly, presence and severity of WMH, lacunes, micro-bleeds and enlarged perivascular spaces (EPVS) were rated according to established protocol, published previously using validated visual scales (Wardlaw et al., 2011, Cordonnier et al., 2009, Potter et al., 2015). These scales for were converted to dichotomous

point scores and summed to create the SVD score (Klarenbeek et al., 2013, Staals et al., 2014, Huijts et al., 2013, Staals et al., 2015). Imaging evidence of infarcts in the cortical or subcortical regions were also recorded using a validated stroke lesion rating scale (Wardlaw and Sellar, 1994). Superficial and deep atrophy scores were coded separately using a valid template (Farrell et al., 2009) and summed to give a total score and then dichotomised into 'none or mild' and 'moderate or severe'.

Quantitative structural image analysis was conducted on the LBC 1936 and Simpson cohort only. This included measurements of volumes of the intracranial compartment (ICV), whole brain (which was corrected for ICV) and total WMH volume. In both cohorts whole brain volume was also calculated as a percentage of the ICV and used as a marker of global brain atrophy (higher percentage indicating less atrophy). The volumes of the ventricles, grey matter, normal appearing white matter, hippocampi and cerebral spinal fluid were calculated in the LBC 1936 and volumes of the brain sub regions (frontal and temporal lobe, amygdala hippocampal complex and corpus collosum) were calculated in the Simpson cohort. Tissue segmentation was done using a semiautomatic segmentation tool MCMxxxVI. Analysis were performed using Analyze^{TM} software. All segmented images were visually inspected and manually edited any incorrectly classified tissues.

4.2.3 Psychiatric measurements

In the STRADL study depressive symptoms were measured using the self-report version of the Quick Inventory for Depressive Symptomology (QIDS-16) (Rush et al., 2003). Symptoms of anxiety were measured using the Hospital Anxiety and Depression Scale anxiety subscale (HADS-A) (Zigmond and Snaith, 1983) . Both were administered on the same day as the MRI scan.

In the Dutch Famine Birth Cohort, the LBC 1936 and the Simpson cohort symptoms of depression and anxiety were measured using the depression and anxiety subscales on the HADS (HADS-D, HADS-A) which were administered on or near the day of the MRI scan.

A total of 280, 151, 1091 and 130 participants in STRADL, the Dutch Famine Birth Cohort, the LBC 1936 and the Simpson cohort respectively completed the mood scales. However this chapter only includes only participants who also completed the MRI part of the study (see Chapter 3 for more detail).

4.2.4 Statistical analysis

Descriptive characteristics were calculated using means and standard deviations (SD), medians and interquartile ranges or counts and percentages as appropriate. Differences in demographic characteristics and symptoms of depression and anxiety were calculated using chi-squared tests.

Total cSVD score was dichotomised into 0-1 ("no or mild disease") and 2-4 ("moderate-severe disease"). Scores on the QIDS-16 (16 items, range 0-27), HADS-D (seven items, range 0-21) and HADS-A (seven items, range 0-21) were analysed separately. Each cohort was analysed separately and then meta-analysed to maximise sample size.

In all cohorts linear regression was used to examine associations between individual dichotomised cSVD markers (in all cohorts) and total and regional brain volumes (LBC 1936 and Simpson cohort only) and scores on the QIDS-16, HADS-D and HADS-A scales. All analyses were adjusted for age, sex, cognition and main vascular risk factors (hypertension, smoking behaviour) and adult SES. Bootstrapping was used for analyses with non-normally distributed residuals.

Regression analyses were performed using SPSS version 22 (IBM Corp, 2013) and meta-analyses were performed using the package metacor for R v3.3.2 (R Core Team, 2016).

4.3 Results

Demographic and key characteristics of all participants are displayed in Table 4.1.

STRADL (n=253) had a mean age of 62.3 (SD 1.6) and were 45% male. The Dutch famine cohort (n=118) had a mean age of 67.5 (SD 0.9) and were 44% male. The LBC 1936 (n=685) had a mean age of 72.7 (SD 0.7) and were 53% male. The Simpson cohort (n=110) had a mean age of 78.4 (SD 1.5) and were 49% male. The overall sample had a mean age of 72.7 (SD 2.8) and were 49% male.

Total cSVD burden increased with increasing age of the cohorts, however overall few had high cSVD scores (Table 4.1B). Furthermore, the number of participants with microbleeds (Dutch Famine Birth cohort n=16; Simpson cohort n= 11), lacunes (Dutch Famine Birth cohort n=26; Simpson cohort n= 27) and infarcts (STRADL= 9; Dutch Famine Birth cohort n=22; Simpson cohort n= 10) were low,

Scores on the HADS increased with increasing age of the cohorts but median HADS scores were low in all cohorts (table 4.1A). Participants in the Simpson cohort had significantly higher scores on the HADS-A ($\chi^2(3) = 6.7$, $p=0.04$) and HADS-D ($\chi^2(2) =42.74$, $p<0.001$) compared to the other cohorts.

Table 4.1: (A**)** Demographic and health characteristics and (B) imaging characteristics of STRADL, the Dutch Famine Birth cohort, the Lothian Birth cohort and the Simpson cohort

(A)

	STRADL		**Dutch Famine**		**LBC1936**		**Simpsons**	
	Total n	n (%)	Total n	n (%)	Total n	n (%)	Total n	n (%)
Age (y) at MRI, mean (SD)	253	62.3 (1.6)	118	67.5 (0.9)	685	72.7 (0.7)	110	78.4 (1.5)
Sex, male	253	114 (45.1)	118	52 (44.1)	685	361 (52.7)	110	33 (30)
Health covariates: history								
Hypertension	251	29 (11.6)	117	62 (53.0)	685	336 (49.1)	110	49 (44.6)
Diabetes	251	3 (1.2)	118	24 (20.3)	685	72 (10.5)	110	7 (6.4)
Hypercholesterolemia			117	56 (47.9)	685	287 (41.9)	-	-
Smoking history	252		118		685		110	
Current smoker		35 (13.9)		13 (11.0)		56 (8.2)		8 (7.3)
Ex-smoker		84 (33.3)		59 (50.0)		306 (44.7)		52 (47.3)
Never smoked		133 (52.8)		46 (39.0)		323 (47.2)		50 (45.5)
History of stroke	253	4 (1.6)	117	3 (2.6)	685	47 (6.9)	110	16 (14.6)
BMI, mean (SD)			118	28.8 (4.9)	684	27.8 (4.4)	110	27.4 (4.2)
Adult SES (manual)	249	53 (21.3)	118	44 (37.3)	674	141 (20.9)	110	64 (58.2)
Psychiatric measures								
QIDS-16	253	3 (4)	-	-	-	-	-	-
HADS-D, median (IQR)	-	-	118	1 (2)	685	3 (3)	110	4 (3)
HADS-A, median (IQR)	253	3 (4.0)	118	4 (4)	685	4 (4)	110	5 (4)

SES: socioeconomic status; QIDS-16: Quick inventory Depressive Symptomology; HADS-D: Hospital Anxiety and Depression scale, depression subscale; HADS-A: Hospital Anxiety and Depression scale, anxiety subscale. – is used where data were not available

(B)

Variable		STRADL		Dutch Famine		LBC1936		Simpsons	
		Total n	n (%)	Total n	n (%)	Total n	n (%)	Total n	n (%)
Visual ratings									
Total cSVD score		241		114		680		96	
	0		48 (19.9)		52 (45.6)		302 (44.4)		12 (12.5)
	1		116 (68.0)		35 (30.7)		249 (36.6)		53 (55.2)
	2		67 (27.8)		16 (14.0)		98 (14.4)		20 (20.8)
	3		8 (3.3)		9 (6.0)		27 (4.0)		8 (8.3)
	4		2 (0.8)		2 (1.3)		4 (0.6)		3 (3.1)
Moderate/severe cSVD		241	77 (32.0)	114	27 (23.7)	680	129 (19.0)	97	31 (32.0)
Moderate/severe WMH		252	40 (15.9)	118	30 (25.4)	685	154 (22.5)	110	27 (24.6)
Moderate/severe EPVS		249	193 (77.5)	114	28 (24.6)	680	276 (25.3)	110	83 (75.5)
1+ Lacune		253	18 (7.1)	118	26 (22)	680	33 (4.9)	110	27 (24.5)
1+ CMB		246	42 (17.1)	117	16 (13.7)	680	79 (11.6)	97	11 (11.3)
Imaging evidence of 1+ infarct		253	9 (3.6)	118	22 (18.6)	685	99 (14.5)	110	10 (7.7)
Moderate/severe atrophy		253	27 (10.7)	118	23 (19.5)	685	189 (27.6)	110	64 (58.2)
Brain volumes									
Whole brain volume (mm^3), mean (SD)		-	-	-	-	657	990,322.7 (89401.9)	110	1,137,480.3 (98,056.8)
ICV (mm3), mean (SD)		-	-	-	-	659	1,438,223.1 (133870.1)	95	1,454,751.5 (123,117.8)
WMH volume (mm3), median (IQR)		-	-	-	-	656	7,896.0 (11531.0)	107	25,755.4 (27,166.0)

cSVD: cerebral small vessel disease; WMH: white matter hyperintensities; EPVS: enlarged perivascular spaces; CMB: cerebral microbleed. – is used where data were not available.

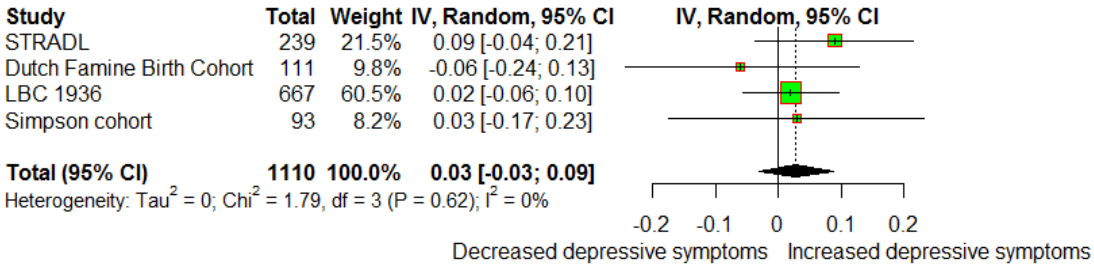
4.3.1 cSVD and symptoms of depression and anxiety

4.3.1.1 Symptoms of depression

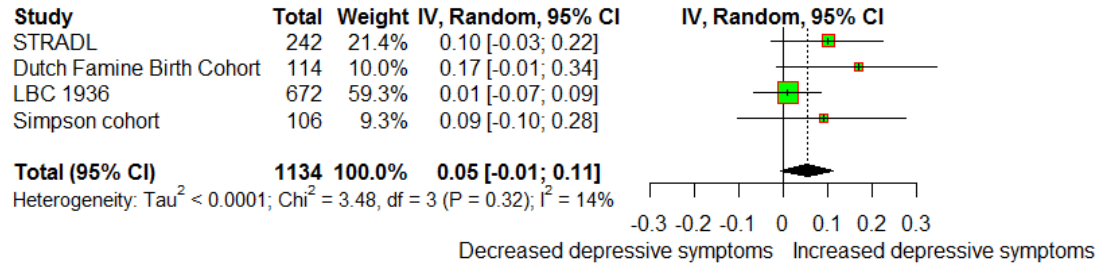
Total cSVD score, WMH burden, lacunes, microbleeds and EPVS were not associated with scores on the QIDS-16 in STRADL or HADS-D in the Dutch Famine Birth cohort, LBC 1936 or the Simpson cohort. Total WMH volume was associated with increased scores on the HADS-D in the Simpson cohort (β= 0.24, p=0.01, Figure 4.1 C). Across all cohorts the presence of one or more infarct and moderate/severe atrophy were associated with increased scores on the HADS-D (β=0.08, p=0.01; β= 0.09, p=0.02, Figure 4.1 F,H). Associations between HADS-D and infarcts were attenuated when history of stroke was added as a covariate (β= 0.09, p=0.04). History of stroke was associated with higher depressive symptoms in the LBC 1936 only (β= 0.09, p=0.02).

Figure 4.1 (A-H): Associations between cSVD and depressive symptoms on the QIDS-16 or HADS-D. Meta-analysis of all cohorts.

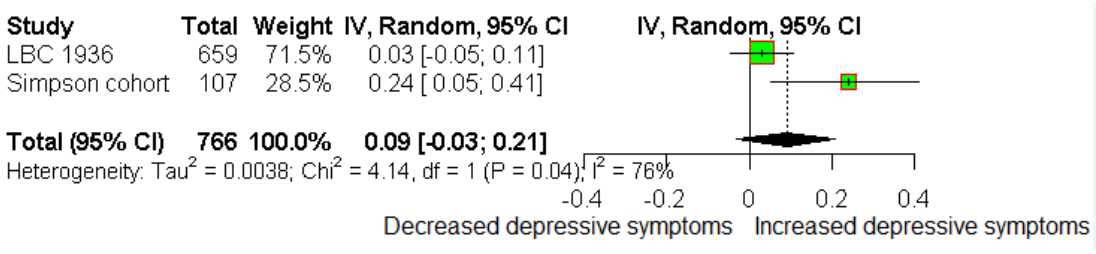
(A) Presence of moderate or severe total cSVD burden



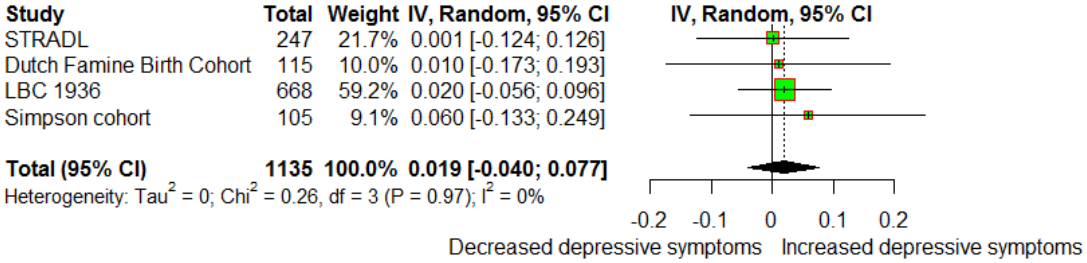
(B) Presence of moderate or severe WMH burden



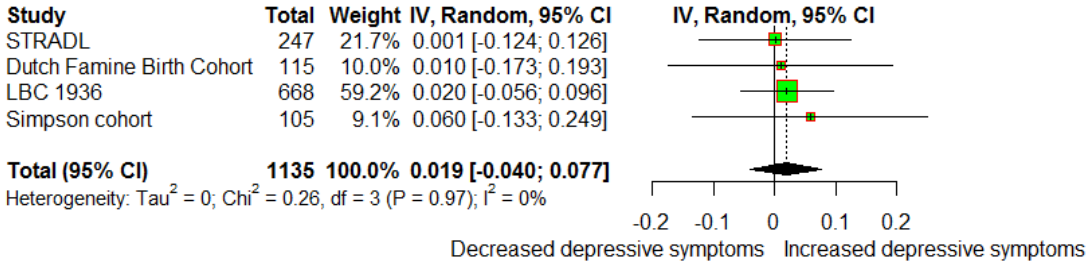
(C) Total WMH volume



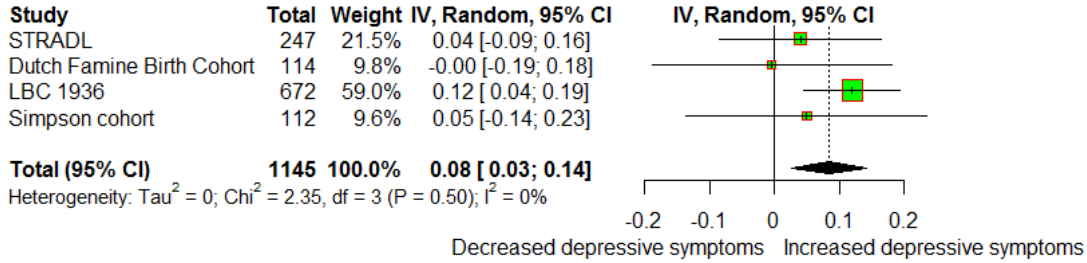
(D) Presence of one or more lacune



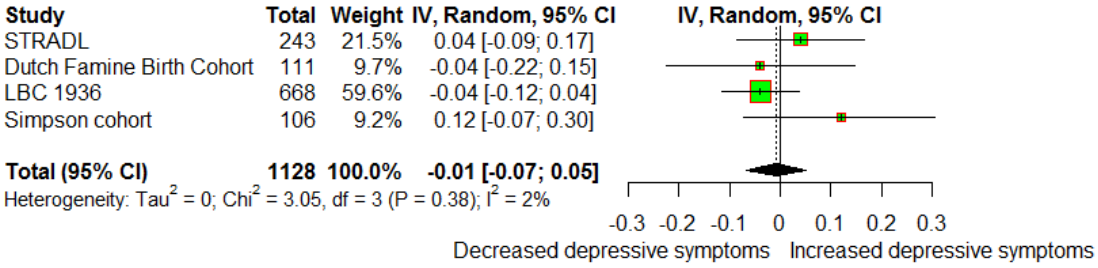
(E) Presence of one or more microbleed



(F) Presence of one or more infarct



(G)Presence of moderate or severe EPVS



(H) Presence of moderate or severe atrophy

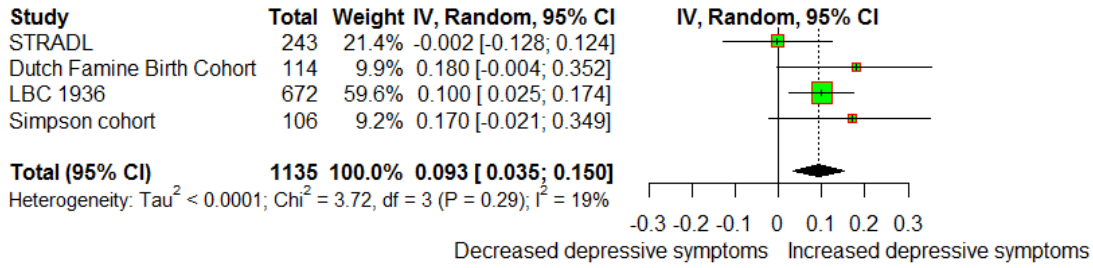


Figure 4.1 (A-H): Associations between cSVD and depressive symptoms on the QIDS-16 or HADS-D 16. Meta-analysis of all cohorts.

Table 4.2: Linear regression analysis of markers of cSVD and depressive symptoms on the or QIDS-16 and HADS-D subscale in STRADL, the Dutch Famine Birth cohort, the LBC 1936 and Simpson cohort

	STRADL			Dutch Famine Birth Cohort			LBC 1936			Simpson cohort		
	QIDS-16			HADS-D								
	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Moderate/severe total cSVD score	0.09	0.48	0.19	-0.06	0.73	0.55	0.02	0.22	0.72	0.03	0.48	0.81
Moderate/severe WMH	0.10	0.67	0.16	0.17	0.78	0.14	0.01	0.21	0.91	0.09	0.53	0.36
Moderate/severe EPVS	0.04	0.45	0.47	-0.04	0.63	0.68	-0.04	0.17	0.39	0.12	0.53	0.22
1+ Lacune	0.001	0.82	0.99	0.01	0.72	0.88	0.02	0.39	0.51	0.06	0.55	0.57
1+ CMB	-0.04	0.01	0.47	-0.02	0.85	0.84	0.04	0.27	0.31	0.04	0.81	0.74
Imaging evidence of 1+ infarct*	0.04	1.26	0.56	-0.004	0.84	0.97	**0.12**	**0.28**	**0.02**	0.05	0.85	0.62
Moderate/severe atrophy	-0.002	0.64	0.97	0.18	1.12	0.20	**0.10**	**0.17**	**0.01**	0.17	0.6	0.13

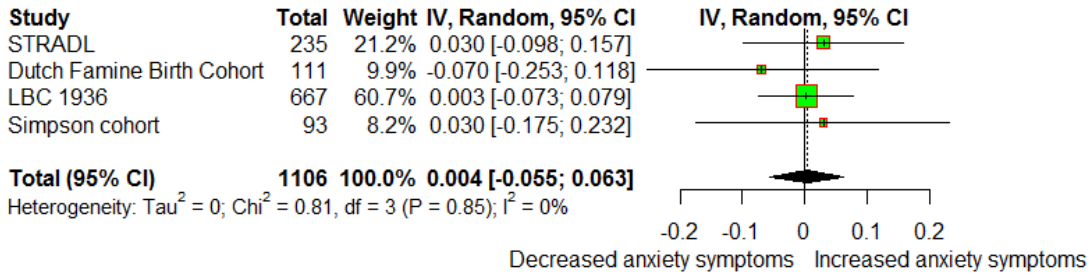
cSVD: cerebral small vessel disease; WMH: white matter hyperintensities; EPVS: enlarged perivascular spaces; CMB: cerebral micro-bleed; QIDS-16: Quick Inventory of Depressive Symptomology; HADS-D: depression subscale; All betas are standardised. All analyses are adjusted for age, sex, hypertension, smoking behaviour, adult SES and cognition. * This analysis includes participants with cortical and subcortical symptomatic and non-symptomatic infarcts. For analyses controlling for a history of stroke see text. SEs are based on 1000 bootstrap samples.

4.3.1.2 Symptoms of anxiety

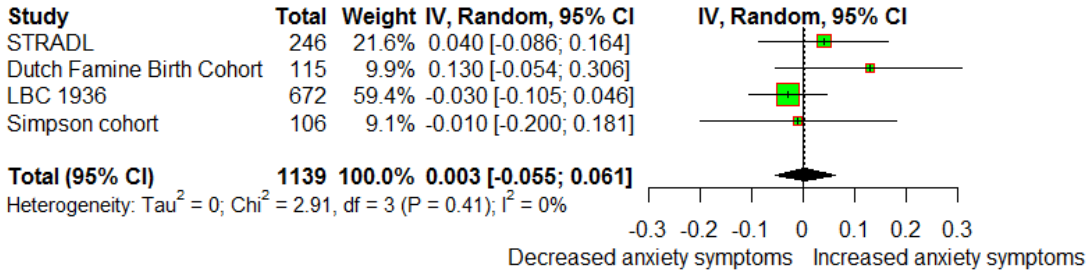
No cSVD markers or history of stroke were associated with scores on the HADS-A subscale in any of the cohorts or in the meta-analysis (Table 4.3, Figures 4.2 A-G).

Figure 4.2 (A-G): Associations between cSVD and symptoms of anxiety on the HADS-A. Meta-analysis of all cohorts

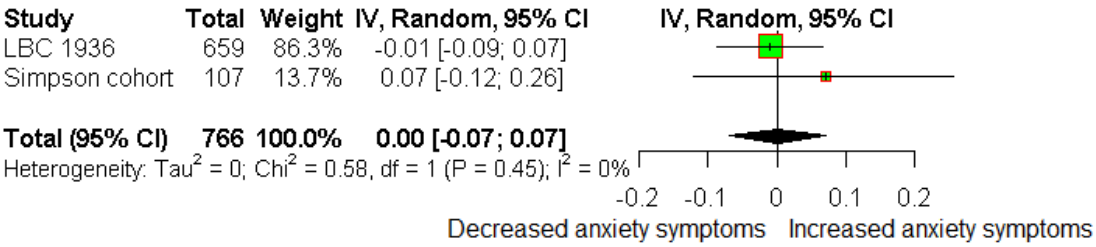
(A) Presence of moderate or severe total cSVD burden



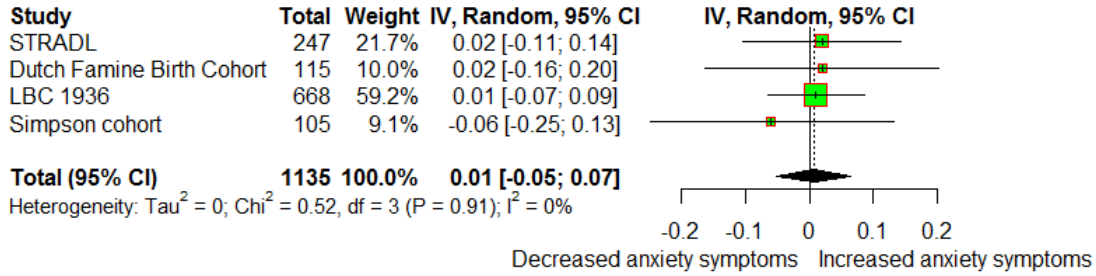
(B) Presence of moderate or severe WMH burden



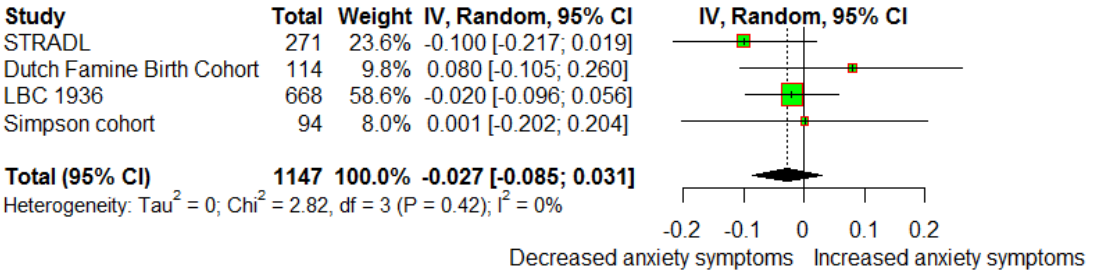
(C) WMH volume



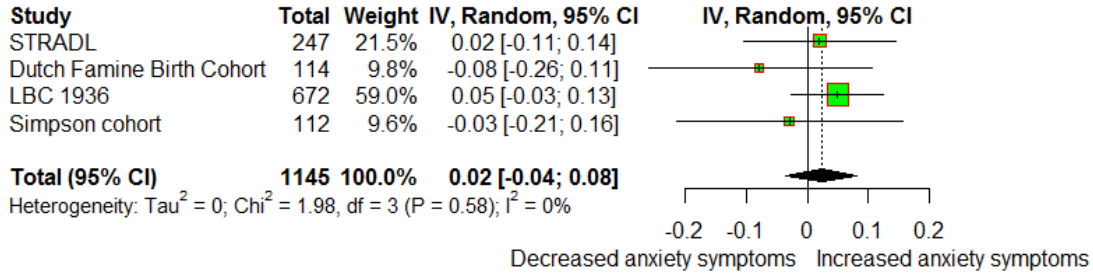
(D) Presence of one or more lacune



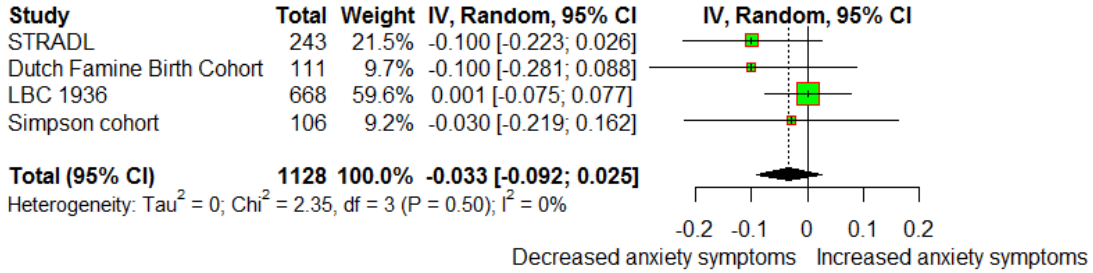
(E) Presence of one or more microbleed



(F) Presence of one or more infarct



(G) Presence of moderate or severe EPVS



(H) Presence of moderate or severe atrophy

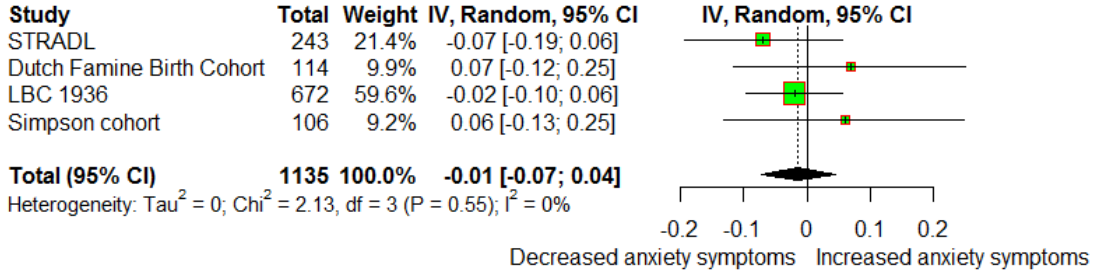


Figure 4.2 (A-G): Associations between cSVD and symptoms of anxiety on the HADS-A. Meta-analysis of all cohorts

Table 4.3 Linear regression analysis of markers of cSVD and score on the HADS-A subscale in STRADL, the Dutch Famine Birth cohort, the LBC 1936 and Simpson cohort

	STRADL			Dutch Famine Birth Cohort			LBC 1936			Simpson cohort		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Moderate/severe total cSVD score	0.03	0.40	0.66	-0.07	0.75	0.55	0.003	0.29	0.93	0.03	0.66	0.81
Moderate/severe WMH	0.04	0.51	0.54	0.13	0.75	0.24	-0.03	0.29	0.46	-0.01	0.70	0.96
Moderate/severe EPVS	-0.10	0.44	0.10	-0.10	0.63	0.31	0.001	0.24	0.96	-0.03	0.74	0.78
1+ Lacune	0.02	0.71	0.68	0.02	0.66	0.81	0.01	0.48	0.70	-0.06	0.62	0.44
1+ CMB	-0.10	0.0001	0.06	0.08	0.93	0.45	-0.02	0.35	0.63	0.001	1.11	0.998
Imaging evidence of 1+ infarct*	0.02	0.99	0.74	-0.08	0.73	0.46	0.05	0.36	0.21	-0.03	0.83	0.68
Moderate/severe atrophy	-0.07	0.66	0.27	0.07	0.83	0.51	-0.02	0.23	0.55	0.06	0.71	0.56

cSVD: cerebral small vessel disease; WMH: white matter hyperintensities; EPVS: enlarged perivascular spaces; CMB: cerebral micro-bleed; HADS-A: anxiety subscale;: All betas are standardised. All analyse s are adjusted for age, sex, hypertension, smoking behaviour, adult SES and cognition. * This analysis includes participants with cortical and subcortical symptomatic and non-symptomatic infarcts.

4.3.2 Brain volumes and symptoms of depression

4.3.2.1 Symptoms of depression

Total brain volumes

Across the LBC 1936 and Simpson cohort more global brain atrophy and lower whole brain volume were associated with higher scores on the HADS-D (β= -0.18, p=0.001; β= -0.17, p=0.001, Table 4.4, Figures 4.3 A-B)

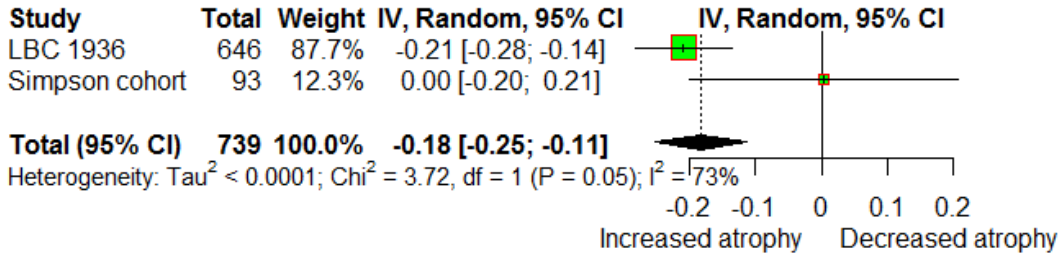
Table 4.4: Linear regression analysis of whole brain volumes and depressive symptoms on the HADS-D in the LBC 1936 and Simpson cohort

Brain volumes (mm^3)	**LBC 1936**			**Simpson cohort**		
	β	**SE**	**p**	β	**SE**	**p**
Whole brain atrophy	**-0.21**	**0.05**	**0.001**	-0.01	0.08	0.9
Whole brain volume	**-0.22**	**4.55**	**0.001**	-0.002	0.25	0.99
ICV	-0.04	0.001	0.44	-0.07	0.001	0.59

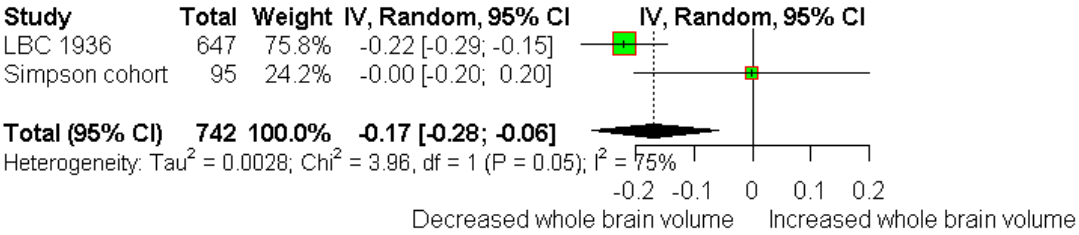
ICV: Intracranial volume; HADS-D: depression subscale. All analyses are adjusted for age, sex, hypertension, smoking behaviour, adult SES and cognition. Whole brain volume is adjusted for ICV. Standard errors and p values for HADS-D are based on 1000 bootstrap samples.

Meta-analysis of cohorts

(A) Global brain atrophy



(B) Whole brain volume (corrected for ICV)



(C) ICV

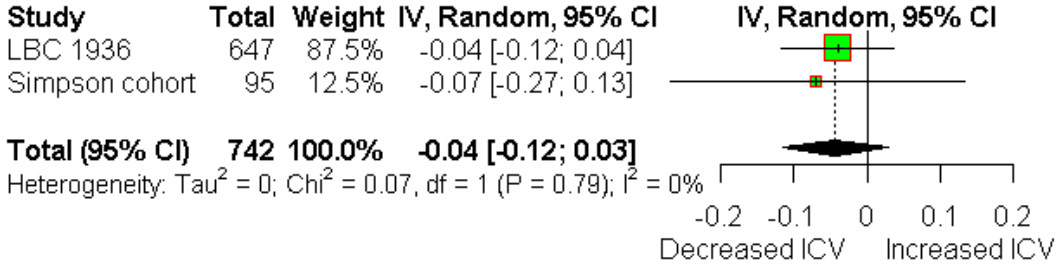


Figure 4.3: Associations between whole brain volumes and depressive symptoms on the HADS-D. Meta-analysis of the LBC 1936 and the Simpson cohort.

Regional brain volumes

Increased CSF volume, decreased grey matter volume and decreased normal appearing white matter volume were associated with increased depressive symptoms on the HADS-D in the LBC 1936 (β= 0.22, p=0.001; β=- 0.12, p=0.01; β= -0.13, p=0.004, Table 4.5). Regional brain volumes were not associated with scores on the HADS-D in the Simpson cohort (Table 4.5).

Table 4.5: Linear regression analysis of regional brain volumes and symptoms of depression and anxiety on the HADS-D and HADS-A in (a) the LBC 1936 and (b) the Simpson cohort

(A)

Brain volumes (mm3)	**HADS-D**			**HADS-A**		
	β	**SE**	**p**	β	**SE**	**p**
Right hippocampal volume	-0.01	0.001	0.84	-0.01	0.001	0.81
Left hippocampal volume	0.06	0.001	0.13	0.03	0.001	0.47
CSF volume	**0.22**	**3.78**	**0.001**	-0.05	5.46	0.27
Grey matter volume	**-0.12**	**5.31**	**0.01**	0.05	7.14	0.21
Normal appearing white matter volume	**-0.13**	**5.12**	**0.004**	-0.02	7.13	0.61

HADS-D: depression subscale; HADS-A: anxiety subscale; CSF: cerebral spinal fluid; All analyses are adjusted for age, sex, hypertension, smoking behaviour, adult SES and cognition. All brain volume are adjusted for ICV. SEs and p values for HADS-D based on 1000 bootstrap samples

(B)

Brain volumes (mm3)	**HADS-D**			**HADS-A**		
	β	**SE**	**p**	β	**SE**	**p**
Frontal lobe volume (mm3)	0.06	0.26	0.60	-0.01	0.33	0.94
Temporal lobe volume (mm3)	0.07	0.3	0.59	-0.05	0.36	0.63
AHC volume (mm3)	-0.18	0.22	0.05	-0.12	0.34	0.24
Ventricular volume (mm3)	0.05	0.001	0.57	0.11	0.001	0.30
Corpus callosum area (mm2)	-0.02	0.003	0.89	-0.05	0.004	0.61

HADS-D: depression subscale; HADS-A: anxiety subscale; AHC: Amygdala hippocampal complex; All analyses are adjusted for age, sex, hypertension, smoking behaviour, adult SES and cognition. All brain volume are adjusted for ICV. SEs and p values for HADS-D based on 1000 bootstrap samples

4.3.2.2 Symptoms of anxiety

Total brain volumes

Across both cohorts higher ICV was associated with lower scores on the HADS-A (β= -0.12, p=0.001). Whole brain volumes were not associated with scores in the HADS-A in the Simpson cohort (Table 4.6, Figures 4.4 A-C).

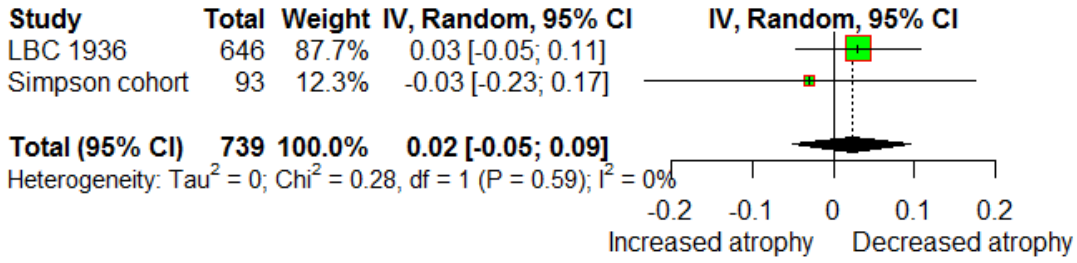
Table 4.6: Linear regression analysis of whole brain volumes and symptoms of anxiety on the HADS-A in the LBC 1936 and Simpson cohort

Brain volumes (mm^3)	**LBC 1936**			**Simpson cohort**		
	β	**SE**	**p**	β	**SE**	**p**
Whole brain atrophy	0.03	0.06	0.53	-0.03	0.11	0.8
Whole brain volume	0.01	5.91	0.81	-0.07	0.35	0.54
ICV	**-0.11**	**0.001**	**0.03**	-0.25	0.001	0.06

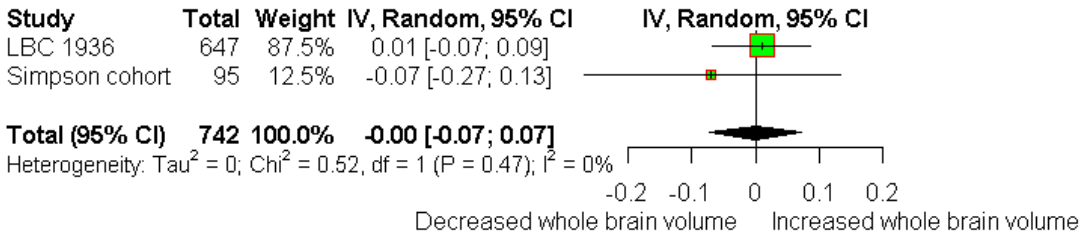
ICV: Intracranial volume; HADS-A: anxiety subscale; All analyses are adjusted for age, sex, hypertension, smoking behaviour, adult SES and cognition. Whole brain volume is adjusted for ICV.

Meta-analysis of cohorts

(A) Global brain atrophy



(B) Whole brain volume (corrected for ICV)



(C) ICV

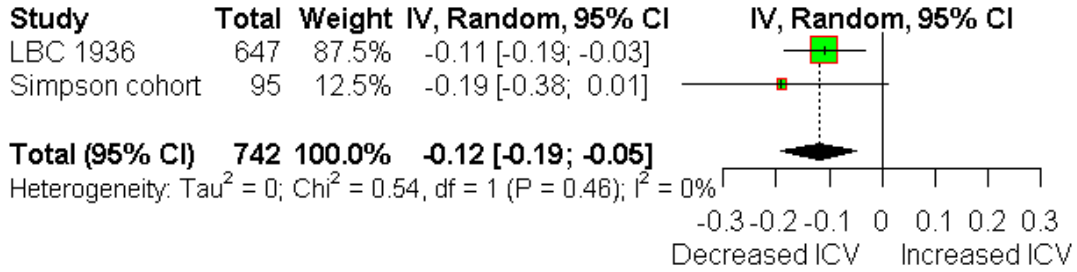


Figure 4.4: Associations between whole brain volumes and symptoms of anxiety on the HADS-A. Meta-analysis of the LBC 1936 an Simpson cohort

Regional brain volumes

Regional brain volumes were not associated with symptoms of anxiety on the HADS-A in the LBC 1936 or the Simpson cohort (Table 4.5).

4.4 Discussion

The present study investigated the associations between structural brain changes and symptoms of anxiety and depression in four community dwelling cohorts. There were three main findings; firstly, higher WMH volumes were associated with increased depressive symptoms; secondly, infarcts were associated with increased depressive symptoms; thirdly, increased cerebral atrophy was associated with increased depressive symptoms. This association was statistically significant for visually rated atrophy and semi-automated measurements of whole brain volume, whole brain volume as a percentage of the ICV and global grey and white matter volumes. These associations were independent of vascular risk factors, cognition and adult SES. There were no consistent associations between structural brain changes and symptoms of anxiety.

The first finding supports the wealth of literature linking white matter disease and depressive symptoms in older adults. Several meta-analyses have concluded that WMHs are associated with late life depression (van Agtmaal et al., 2017, Herrmann et al., 2008, Wang et al., 2014a, Arnone et al., 2012). The most recent and largest meta-analysis of 33 studies (mean age 66) found that higher total WMH burden was associated with a 29% increase in incident depression (van Agtmaal et al., 2017). The present study did not find associations between WMH and depressive symptoms in all cohorts. This may be due to several reasons. Firstly all analyses were adjusted for vascular risk factors, adult SES and cognition, whereas less than half of the studies included in the meta-analysis by van Agtmaal et al adjusted for these factors. Secondly, participants in the current study were community dwelling older adults who were relatively healthy with very low depressive symptoms. The association between WMH and depressive symptoms was only apparent in the oldest of the four cohorts, the Simpson cohort, who had the highest WMH burden and significantly more depressive symptoms compared to the other cohorts. It may be that associations between cSVD and depressive symptoms are stronger in older people with higher WMH burden and more severe depression.

In younger relatively healthy participants diffusion tensor imaging (DTI) may be a more sensitive method of measuring early white matter structural damage, compared to the Fazekas scale or WMH volume (Pasi et al., 2016). DTI measures the diffusion of water molecules in vivo and uses two quantitative parameters, the mean diffusivity (<D>)

and fractional anisotropy (FA), to indicate the amount of tissue damage evident in an individual. Low values of <D> and high values of FA indicate intact healthy tissue. Studies using both DTI and conventional MRI found significant associations between white matter integrity and depressive symptoms in older subjects (mean age 68 and 75) but found no association between WMH volume and depression (Pasi et al., 2016, Lamar et al., 2010). Previous research in the LBC 1936 and other cohorts have consistently reported associations between depressive symptoms and white matter integrity in areas important for cognitive and affective processing (McIntosh et al., 2012, Wen et al., 2014, Pasi et al., 2016, Lamar et al., 2010). Meta-analysis has shown that compared with healthy controls, patients with late-life depression had lower FA across multiple regions including the dorsolateral prefrontal cortex, uncinate fasciculus and cingulum (Wen et al., 2014). Disrupted connectivity of white matter tracts in the frontalstriatal and limbic networks may lead to emotional dysregulation and increased depressive symptoms (Wen et al., 2014).

This chapter did not examine WMHs in different brain regions, however it is possible that WMHs occurring in certain anatomic locations may differentially associate with depressive symptoms. For example, stronger associations have been reported between deep WMH and depression compared to periventricular or total WMH burden (Wang et al., 2014a), although this is not supported by all studies (Tully et al., 2017). Other studies have reported stronger associations between WMHs in the frontal regions and depression (Wang et al., 2014a).

This chapter examined multiple markers of cSVD and symptoms of depression and anxiety. There were no associations between EPVS, lacunes or microbleeds and symptoms of depression or anxiety in any of the cohorts. Fewer studies have examined markers of cSVD other than WMH. In line with the current findings one previous study found no association between EPVS burden and depressive symptoms (van Sloten et al., 2015). Some studies have found no association between lacunar infarcts and depressive symptoms (Pasi et al., 2016, O'Brien et al., 2006). However others have reported that lacunar infarcts are associated with increased depressive symptoms (Grool et al., 2011, Direk et al., 2016) and increased DSMIV diagnosis of MDD (Direk et al., 2016). Two population based studies found no association between microbleeds and depressive symptoms (van Sloten et al., 2015, Direk et al., 2016). However in two hospital based studies of stroke patients microbleeds were associated with a DSM-IV diagnosis of MDD (Tang et al., 2011a,

Tang et al., 2011b), and one population study (Direk et al., 2016), which suggests that microbleeds may be a specific vascular pathology only seen in the most severe form of depression.

In the LBC 1936, presence of one or more infarct was associated with more depressive symptoms. This analysis included participants with cortical and subcortical symptomatic and non-symptomatic infarcts. Depression or depressive symptoms are common in people with a history of stroke, occurring in almost a third of patients during the first 5 years (Hackett and Pickles, 2014). In the present study those in the LBC 1936 with a history of stroke had significantly higher depressive symptoms than those with no history of stroke. In order to determine whether the associations between infarcts and depression was driven by these individuals, history of stroke was added as a covariate. This attenuated the association between infarcts and depressive symptoms but it remained statistically significant. Anxiety is also common after stroke occurring in 20-25% of patients (Campbell Burton et al., 2013), However there was no association between infarcts or history of stroke and anxiety in the current analysis.

There were significant associations between visually rated atrophy, whole brain volume measured as a percentage of the ICV, whole brain volume, CSF volume, global grey and white matter volume and depressive symptoms. Previous longitudinal studies have suggested that larger brains are protective against later development of depression (Qiu et al., 2017, van Sloten et al., 2015).One large community based longitudinal study with a follow up of 7 years (n= 1,400 mean age ~ 60 years), found that larger total cerebral brain volume was associated with lower risk of depression, defined as ≥ 16 on the Centre for Epidemiologic Studies of Depression (CES-D) scale (OR 0.78, 95% CI 0.65-0.92) (Qiu et al., 2017). Similar findings were reported in another longitudinal study with a follow up of 5 years (mean age 75 years) (van Sloten et al., 2015). Cross sectional studies have reported mixed results. One study found a that those with a DSM-IV diagnosis of depression (mean age 72 years) had significantly higher visually rated atrophy compared to non-depressed older adults (Lin et al., 2005). Other cross sectional studies (Qiu et al., 2017, Sheline et al., 2008), including one pathology study (Nunes et al., 2017), found no association between total brain volume and late life depression and have suggested that morphological changes in late life depression are regional rather than global. Meta-analyses of region of interest and voxel based methods have documented reductions in grey matter volumes in the frontal-subcortical and limbic circuitry such as the orbitofrontal

cortex, hippocampus, putamen thalamus and amygdala (Sexton et al., 2013b, Du et al., 2014, Boccia et al., 2015) in patients with late life depression The present study found no association between regional brain volumes and depressive symptoms.

Previous studies have either used clinical samples and case control designs with older adults with depression and aged matched controls, or have used cut off scores on self-report questionnaires to identify clinically relevant depression. However in older adults subsyndromal depressive symptoms are more common than a diagnosis of major depression (Lyness et al., 1999b) and community samples, like the cohorts used in this Thesis, may be more representative of the general population than purely clinically ascertained samples. Only 11 STRADL participants and less than 20 participants across the Dutch Famine Birth cohort, the LBC 1936 and the Simpson cohort met the QIDS-16 or HADS-D threshold for clinical depression. The findings presented in this chapter suggest that changes in whole brain volume and global white and grey matter volume are associated with even low levels of depressive symptoms. Tudorascu and colleagues (2014) examined associations between grey matter volume and subsyndromal depression, in a large community sample. They reported the odds of subsyndromal depression, defined as scoring greater than 10 on CES-D scale, decreased by 15% for every unit increase in grey matter volume after adjustment for confounders (Tudorascu et al., 2014).

A clinical diagnosis of major depression is a strong predictor for impairments in physical functioning and lower quality of life (Rodríguez et al., 2012) but the clinical importance of subsyndromal depression should not be overlooked. A study by Chachamovich et al (2008) assessed a large international sample of older adults and found that a score as low as 2 on the Geriatric Depression Scale (GDS) was associated with lower quality of life and a more negative attitude towards aging (Chachamovich et al., 2008). This suggests that even relatively minor levels of depressive symptoms, such as seen in this study, may be of clinical importance. Furthermore, using depressive symptoms as a continuous rather than dichotomous outcome gives higher statistical power and allows all available data to be explored. Recognising and diagnosing depression and anxiety disorders in older populations may be more difficult than in younger adults. Pachana (2008) argues that the current cohort of older adults may be less comfortable than later generations in discussing their emotions or may see symptoms of depression such as fatigue as inevitable consequences of aging which may lead to underreporting (Pachana, 2008). However,

the HADS has demonstrated good sensitivity and specificity and has been identified as a good screening tool for depression and anxiety in the general population, general practice and psychiatric settings (Bjelland et al., 2002).

Regional brain atrophy and WMHs are associated with both depression and cognitive decline and have been shown to precede the incidence of both disorders by 10 years (Gudmundsson et al., 2015). This shared pathology may explain why depression and dementia often co-exist in older adults (Leyhe et al., 2017). Late-life depression has been described as both a risk factor and a prodrome of dementia, particularly Alzheimer's disease. This may be influenced by the time of life when depression is first experienced. Those who have experienced depression during mid- life may be more likely to develop dementia, particularly vascular dementia whereas depression occurring for the first time in later life may reflect a prodromal stage of dementia, particularly Alzheimer's disease (Barnes et al., 2012). To avoid any confounding by cognitive impairment, the analyses in the present study were adjusted for scores on the Ravens Matrices, MMSE and AH4, tests that evaluate multiple cognitive functions.

The present study had several strengths. Firstly, the rich amount of imaging data- both qualitative and quantitative, allowed examination of several features of CVD and symptoms of anxiety and depression. For example, there were associations between both visually rated atrophy and semi-automated measurements. Secondly, this study adjusted for several confounders including cognition, SES and vascular risk factors. People with depression have been shown to have increased rates of cardiovascular disease, diabetes mellitus, smoking and hypertension. Therefore it is important to control for vascular risk factors when assessing pathologies such as WMH and depressive symptoms. Thirdly, although smaller than some previous studies, the sample size of over 1100 participants is relatively large.

The limitations of the study include that is was cross sectional and therefore it is unclear whether the markers of CVD preceded the depressive symptoms or were a result of depression. However, previous longitudinal studies have found associations between WMH and depression particularly when those with depression at baseline are excluded. Associations between infarcts and depressive symptoms were attenuated when adjusting for participants with a history of stroke. Therefore it is not possible to rule out the possibility that this association was driven by those with a history of stroke. Finally, this study was limited by a concentration of lower cSVD scores in the cohorts. As a result, all MRI markers and total cSVD score were

dichotomised. Therefore the number of lacunes, microbleeds, infarcts and WMH and EPVS score were underrepresented in the score. Future research in participants with more varied cSVD scores could examine whether actual scores on the cSVD scale have stronger associations with depressive symptoms.

This study found that increased brain atrophy and brain infarcts were associated with more depressive symptoms in a sample of community dwelling adults aged 68-82 years. WMH were associated with depressive symptoms but only in the oldest cohort which had the highest WMH burden. These findings suggest that even in healthy older adults those with more brain vascular disease are at increased risk of depressive symptoms. Early identification of high risk groups may lead to earlier treatment and may help prevent depressive symptoms from evolving into a major depressive disorder.

5. Relationship between early life factors and cerebral small vessel disease and brain volumes

5.1 Introduction

Structural brain changes associated with aging include cerebral small vessel disease (cSVD) and volume loss. cSVD can result in subclinical brain changes which are detected on neuroimaging or post mortem (Wardlaw et al., 2013) as white matter hyperintensities, (WMH) lacunes, microbleeds, enlarged perivascular spaces (EPVS) and brain atrophy (Wardlaw et al., 2013). These markers of cSVD commonly occur alongside cerebal atrophy. It is therfore important to include a measure of atrophy when assesing the burden of vascular damage in the brain (Wardlaw et al., 2013). Current brain volume can be measured in-vivo using neuroimaging and the size of the skull vault (intracranial volume) can be used to estimate prior maximum brain size.

Neuroimaging markers of cSVD are common at older ages (Murray and Lopez, 1997, Hachinski, 2007b) and are associated with stroke and dementia (Wardlaw et al., 2013). Risk factors for cSVD and atrophy include increasing age and traditional vascular risk factors, particularly hypertension (Debette and Markus, 2010, Dufouil et al., 2001). However common vascular risk factors together only explain a small proportion of variance in WMH (~2%) (Wardlaw et al., 2014) suggesting that other factors may contribute to cSVD pathology.

These factors may include exposures during early life. The Developmental Origins of Adult Heath and Disease (DOHAD) hypothesis (Barker, 2004) proposes that adverse environmental exposures occurring during gestation can cause permanent changes in foetal development which can result in increased vulnerability to chronic diseases in adulthood due to foetal programming (Barker, 2004). Environmental exposures that cause foetal programming include poor nutrition and stress and may also include other factors that affect the intrauterine environment like maternal age (Fall et al., 2015). Prenatal malnutrition is associated with a higher occurrence of coronary heart disease, diabetes and atherosclerotic lipid profile (Roseboom et al., 2006). High levels of maternal stress are associated with low birth weight, tempermaent and behavioural problems in childhood (Harris and Seckl, 2011) and immune disregulation (Marques et al., 2013). Usually environmental factors affecting foetal growth such as stress and poor nurition (Marques et al., 2013) are hard to measure and anthropometric measures such as birth weight, birth length and head circumference are used as proxy

measures (Wilcox, 2001). Higher maternal age is associated with increased risk of intrauterine growth restriction (Odibo et al., 2006) and low birth weight (Fall et al., 2015) and negative health outcomes such as hypertension (Brion et al., 2008) and diabetes (Gale, 2010).

Less is known about the effects of maternal age, birth weight and prenatal malnutrition on brain structure in later life. Birth weight is associated with white matter integrity (Shenkin et al., 2009) and a few small studies have found an association between malnutrition and brain atrophy (de Rooij et al., 2016), ICV and WMH (Hulshoff Pol et al., 2000). No studies have examined these factors and total cSVD burden.

As well as factors affecting pre-natal growth and development, influences in childhood may also affect later disease risk. The meta-analysis presented in chapter 2 found that lower levels of childhood IQ, childhood socioeconomic status (SES) and education were associated with a 17-39% increased risk of cSVD in later life. However the majority of these studies did not adjust for common vascular risk factors or adult SES. Few studies have examined the effect of these early life factors in combination and many collected childhood factors retrospectively in adulthood. There is therefore a need to examine whether relationships between childhood factors and cSVD persist after adjustment for vascular risk factors, adult SES and other early life factors.

The first aim of the present study was to examine the relationships between (a) birth parameters (mainly maternal age, birth weight, birth length, ponderal index and nutrition) and (b) childhood factors (childhood and premorbid IQ, education and measures of childhood SES) and total and individual markers of cSVD (WMH, lacunes, EPVS, CMBs, atrophy) after adjustment for common risk factors.

The second aim of the present study was to examine the relationships between (a) birth parameters (mainly maternal age, birth weight, birth length and ponderal index and nutrition) and (b) childhood factors (childhood and premorbid IQ, education and measures of childhood SES) and total and regional brain volumes after adjustment for common risk factors.

The hypotheses were that (1) Negative birth factors (e.g. increased maternal age, lower birth weight, birth length and ponderal index) and negative childhood factors (e.g. lower childhood IQ, education and SES) would be associated with increased cSVD or infarcts (2) Negative birth factors (e.g. increased maternal age, lower birth

weight, birth length and ponderal index) and negative childhood factors (e.g. lower childhood IQ, education and SES) would be associated with decreased total and regional brain volumes.

5.2 Methods

The methods for recruitment, measurement of birth and childhood factors and neuroimaging are presented in detail in Chapter 3.

5.2.1 Participants

STRADL

Between 2015 and 2017 309 participants from the Aberdeen Children of the 1950's cohort were recruited for the STRADL study. For the present analysis 11 participants were excluded because they were recruited after the cut-off date and 18 were excluded because they were labelled incorrectly and therefore could not be linked with the childhood data. This left 280 participants with demographic and neuropsychiatric data. Of these 253 participants agreed to MRI scans and 241 had completed MRI sequences.

The Dutch Famine Birth cohort

The current study included a total 151 cohort members. For the MRI part of the study 33 people withdrew due to anxiety of the scanner (n=8), metal in the body (n=15) and not wanting to visit the hospital (n=9). Data was lost for one participant making a total of 118 participants with viable MRI data. In accordance with previous publications this study compared participants who were exposed to famine in early gestation (n=41), those who were conceived after the famine (exposed during preconception) (n=42) those born before the famine who were unexposed in utero (n=35).

The Lothian Birth cohort 1936

At wave 2, 700 participants provided some usable MRI sequences (fifteen were removed for missing sequences). Six hundered and eighty participants had complete MRI sequences and a further 5 had some usable sequences.

The Simpson Cohort

One hundred and thirty people agreed to participate in the study. 115 participants agreed to MRI scans and 110 participants had completed scans.

Participants in all cohorts provided written informed consent and research was approved by Local Research Ethics Committees.

5.2.2 MRI analysis

Details of the methods used to assess cSVD burden and brain volumes are given in chapter 3. Briefly, presence and severity of WMH, lacunes, micro-bleeds and perivascular spaces were rated according to established protocol, published previously using validated visual scales (Wardlaw et al., 2011, Cordonnier et al., 2009, Potter et al., 2015). These scales for were converted to dichotomous point scores and summed to create the SVD score (Klarenbeek et al., 2013, Staals et al., 2014, Huijts et al., 2013, Staals et al., 2015). Imaging evidence of infarcts in the cortical or subcortical regions were also recorded using a validated stroke lesion rating scale (Wardlaw and Sellar, 1994). Superficial and deep atrophy scores were coded separately using a valid template (Farrell et al., 2009), summed to give a total score and dichotomised into 'none or mild' and 'moderate or severe'.

Quantitative structural image analysis was done separately and blind to visual scales in LBC1936 and the Simpson cohort only. In both cohorts this included measurement of whole brain volume as a percentage of the ICV which was used as a measure of global brain atrophy, measurement of the intracranial compartment (ICV), whole brain volume which was corrected for ICV and total WMH volume. The volumes of the ventricles, grey matter, normal appearing white matter, hippocampi and cerebral spinal fluid were calculated in the LBC 1936 and volumes of the brain sub regions (frontal and temporal lobe, amygdala hippocampal complex and corpus collosum) were calculated in the Simpson cohort. Tissue segmentation was done using a semiautomatic segmentation tool MCMxxxVI. Analysis were performed using Analyze^{TM} software. All segmented images were visually inspected and manually edited any incorrectly classified tissues. All brain volumes were corrected for ICV.

5.2.3 Statistical analysis

Descriptive characteristics were calculated using means and standard deviations (SD), medians and interquartile ranges or counts and percentages as appropriate. Differences in early life factors between the four cohorts were analysed using one way ANOVAs and Chi-squared tests where appropriate.

Birth weight and placental weight (grams) were divided by 100 so that odds ratios were expressed per 100g.

Total cSVD score was dichotomised into 0-1 (“no or mild disease”) and 2-4 (“moderate-severe disease”). Associations between early life (birth parameters and childhood factors) and cSVD were examined using multiple logistic regression. Early life factors were analysed separately for each cohort and then those factors which were common to more than one cohort were meta-analysed to maximise sample size.

Due to the sample size of the individual cohorts and the number of and similarities between the early life factors it was not possible to adjust for other early life factors in addition to vascular risk factors in all models. Therefore, each early life factor was first analysed separately and adjusted for age, sex, hypertension, smoking behaviour and adult SES only. Then to assess the independence of early life factors, additional multiple regression analyses were conducted, adjusting for other early life factors in addition to vascular risk factors and adult SES where possible.

In the LBC 1936 and Simpson cohort early life factors and brain volumes were analysed using multiple linear regression analysis with age, sex, hypertension, smoking behaviour and adult SES included as covariates. Data on brain volumes were not available for the other cohorts. Bootstrapping was used in analyses with skewed residuals. Regression analyses were performed using SPSS version 22 (IBM Corp, 2013). Review Manager 5.3 was used to meta-analyse odds ratios using a random effects model. The package metacor for R v3.3.2 (R Core Team, 2016) was used to meta-analyse standardised beta-coefficients.

5.3 Results

Table 5.1 A-C provides descriptive data of each cohort. Associations between early life factors and cSVD are presented in section 5.3.1 beginning with birth factors (section 5.3.1.1) and then childhood factors (section 5.3.1.2). Results are presented by early life factor for each individual cohort and forest plots illustrate results from the meta-analysis of two or more cohorts. Where meta-analysis was not possible, results are presented in a table. All analyses are adjusted for vascular risk factors and adult SES. Secondly, multiple regression analyses of early life factors and cSVD, which additionally adjust for other early life factors, are presented in tables 5.3.3-5.3.4 A-B (section 5.3.1.3). Finally associations between early life factors and total and regional brain volumes are presented in section 5.3.2. This section only contains data from the LBC 1936 and Simpson cohort as brain volumes were not available for the other cohorts. Forest plots illustrate results from the meta-analysis of the LBC 1936 and Simpson cohort for birth factors and brain volumes (section 5.3.2.1) and then childhood factors and brain volumes (section 5.3.2.2).

STRADL (n=253) had a mean age of 62.3 (SD 1.6) and was 45% male. The Dutch famine cohort (n=118) had a mean age of 67.5 (SD 0.9) and was 44% males. The LBC 1936 (n=685) had a mean age of 72.7 (SD 0.7) and was 53% male. The Simpson cohort (n=110) had a mean age of 78.4 (SD 1.5) and was 49% male. The overall sample had a mean age of 70.4 (SD 5.0) and were 48% male.

cSVD: Total cSVD burden increased with increasing age of the cohorts, however overall few had high cSVD scores (table 5.3.1a). Furthermore, the number of participants with micro-bleeds (Dutch Famine Birth cohort n=16; Simpson cohort n= 11), lacunes (STRADL n=18; Dutch Famine Birth cohort n=26; Simpson cohort n= 27) and infarcts (STRADL n=9; Dutch Famine Birth cohort n=22; Simpson cohort n= 10) are low.

Table 5.1 A-C: Demographic and health characteristics (A), early life characteristics (B) and imaging characteristics (C) of the Dutch famine birth cohort, the Lothian Birth Cohort and the Simpson cohort. Information is displayed separately for each cohort and for all 3 cohorts overall.

(A)

	STRADL		Dutch Famine		LBC1936		Simpsons		All	
	Total n	n (%)	Total n	n (%)	Total n	n (%)	Total n	n (%)	Total n	n (%)
Age (y) at MRI, mean (SD)	254	62.3 (1.6)	118	67.5 (0.9)	685	72.7 (0.7)	110	78.4 (1.5)	1167	70.4 (5.0)
Sex, male	254	114 (45.1)	118	52 (44.1)	685	361 (52.7)	110	33 (30)	1167	560 (48.0)
Health covariates: history										
Hypertension	251	29 (11.4)	117	62 (53.0)	685	336 (49.1)	110	49 (44.6)	1163	459 (39.5)
Diabetes	251	3 (1.2)	118	24 (20.3)	685	72 (10.5)	110	7 (6.4)	1164	106 (9.1)
Hypercholesterolemia			117	56 (47.9)	685	287 (41.9)	-	-	802	343 (42.8)
Smoking history	252		118		685		110		1165	
Current smoker		35 (13.8)		13 (11.0)		56 (8.2)		8 (7.3)		112 (9.6)
Ex-smoker		84 (33.1)		59 (50.0)		306 (44.7)		52 (47.3)		501 (43.0)
Never smoked		113 (52.4)		46 (39.0)		323 (47.2)		50 (45.5)		552 (47.4)
History of stroke	253	4 (1.6)	117	3 (2.6)	685	47 (6.9)	110	16 (14.6)	912	66 (7.2)
BMI, mean (SD)	-	-	118	28.8 (4.9)	684	27.8 (4.4)	110	27.4 (4.2)	912	30.0 (4.5)
Adult SES (manual)	249	53 (20.9)	118	44 (37.3)	674	141 (20.9)	110	64 (58.2)	1151	302 (26.2)

SES: socioeconomic status; BMI: body mass index; - is used where data not available

(B)

Variable	STRADL		Dutch Famine		LBC1936		Simpsons		All	
Birth factors										
Maternal age, mean (SD)	-	-	118	27.4 (6.1)	140	28.2 (5.7)	110	28.0 (6.4)	368	27.9 (6.0)
Mother older than 35	253	27 (10.7)	-	-	-	-	-	-	253	27 (10.7)
Mother not married at birth	253	3 (1.2)	118	23 (19.5)	-	-	110	11 (10.0)	481	37 (7.7)
Maternal weight (kg), mean (SD)	-	-	100	68.4 (9.3)	-	-	-	-	100	68.4 (9.3)
Birth weight (g), mean (SD)	-	-	118	3417.5 (503.4)	140	3351.5 (482.1)	110	3333.6 (457.2)	368	3367.3 (481.8)
Low birth weight (<5.5lbs)	253	6 (2.4)	-	-	-	-	-	-	253	6 (2.4)
Birth length (cm), mean (SD)	-	-	118	51.9 (8.0)	79	50.0 (3.3)	107	50.7 (2.8)	304	51.0 (5.6)
Ponderal index	-	-	115	26.2 (2.3)	79	27.3 (5.3)	107	25.8 (4.2)	301	26.3 (4.0)
Preterm	219	5 (2.3)	-	-	77	30 (39.0)	110	14 (12.7)	406	49 (12.1)
Head circumference (cm), mean (SD)	-	-	117	32.8 (1.5)	-	-	-	-	117	32.8 (1.5)
Head circumference to length ratio, mean (SD)	-	-	114	64.7 (2.9)	-	-	-	-	114	64.7 (2.9)
Head circumference to weight ratio, mean (SD)	-	-	117	9.8 (1.4)	-	-	-	-	117	9.8 (1.4)
Placental weight (g), mean (SD)	-	-	-	-	-	-	83	678.3 (145.0)	83	678.3 (145.0)
Placental volume (cm3), mean (SD)	-	-	100	696.2 (259.1)	-	-	-	-	100	696.2 (259.1)
Placental area (cm2), mean (SD)	-	-	104	353.5 (94.8)	-	-	-	-	104	353.5 (94.8)
Placental to weight ratio	-	-	104	10.5 (2.4)	-	-	-	-	104	10.5 (2.4)
Famine exposure			118						118	

Born before the famine	-	-		35 (29.7)	-	-	-	-		35 (29.7)
Exposed in early gestation	-	-		42 (35.6)	-	-	-	-		42 (35.6)
Conceived after the famine	-	-		41 (34.8)	-	-	-	-		41 (34.8)
Childhood factors										
Childhood IQ	246	102.0 (8.9)	-	-	648	100.8 (15.3)	30	101.7 (14.5)	924	101.3 (13.9)
Premorbid IQ	254	31.8 (4.0)	-	-	683	34.4 (8.1)	110	30.0 (7.9)		
Education										
Mean years of education	253	12.7 (2.9)	-	-	685	10.8 (1.1)	110	10.3 (2.2)	1048	10.9 (1.3)
Low vs high level of education	253	156 (61.7)	118	74 (62.7)	685	491 (71.7)	110	89 (80.9)	1166	625 (53.6)
No qualifications (vs O level and above)	253	31 (12.3)	-	-	683	119 (17.4)	-	-	913	132 (14.5)
Childhood SES										
Manual Father's occupation (vs non-manual)	240	163 (67.9)	96	64 (66.7)	627	465 (74.2)	110	97 (88.2)	1073	789 (73.5)
Father's years of education, mean (SD)	-	-	-	-	538	10.0 (2.2)	-	-	-	-
Outdoor toilet	-	-	-	-	684	78 (11.4)	110	6 (5.6)	794	84 (10.6)
Number of people sharing a toilet, mean (SD)	-	-	-	-	679	5.28 (2.5)	110	5.6 (3.3)	789	5.3 (2.7)
Overcrowding index, mean (SD)	-	-	-	-	682	1.36 (0.8)	110	1.4 (0.7)	792	1.4 (0.8)

(C)

Variable	STRADL		Dutch Famine		LBC1936		Simpsons		All	
	Total n	n (%)	Total n	n (%)	Total n	n (%)	Total n	n (%)	Total n	n (%)
Visual ratings										
Total SVD score	241		114		680		96		1108	
0		48 (19.9)		52 (45.6)		302 (44.4)		12 (12.5)		404 (36.5)
1		116 (48.1)		35 (30.7)		249 (36.6)		53 (55.2)		446 (40.3)
2		67 (27.8)		16 (14.0)		98 (14.4)		20 (20.8)		198 (17.9)
3		8 (3.3)		9 (6.0)		27 (4.0)		8 (8.3)		50 (4.5)
4		2 (0.8)		2 (1.3)		4 (0.6)		3 (3.1)		10 (0.9)
Moderate/severe cSVD	241	77 (32.0)	114	27 (23.7)	680	129 (19.0)	97	31 (32.0)	1131	264 (23.3)
Moderate/severe WMH	252	40 (15.9)	118	30 (25.4)	685	154 (22.5)	110	27 (24.6)	1165	251 (21.5)
Moderate/severe EPVS	249	193 (77.5)	114	28 (24.6)	680	276 (25.3)	110	83 (75.5)	1153	580 (50.3)
1+ Lacune	253	18 (7.1)	118	26 (22)	680	33 (4.9)	110	27 (24.5)	1156	103 (8.9)
1+ CMB	246	42 (17.1)	117	16 (13.7)	680	79 (11.6)	97	11 (11.3)	1137	148 (13.0)
Imaging evidence of 1+ infarct	253	9 (3.6)	118	22 (18.6)	685	99 (14.5)	110	10 (7.7)	1166	140 (12.0)
Moderate/severe atrophy	253	27 (10.7)	118	23 (19.5)	685	189 (27.6)	110	64 (58.2)	1141	425 (37.2)
Brain volumes										
Whole brain volume (mm3), mean (SD)	-	-	-	-	657	990,322.7 (89401.9)	110	1,137,480.3 (98,056.8)	767	1,011,427.4 (1,04292.4)
ICV (mm3), mean (SD)	-	-	-	-	659	1,438,223.1 (133870.1)	95	1,454,751.5 (123,117.8)	754	1,440,305.6 (1,32599.4)
WMH volume (mm3), median (IQR)	-	-	-	-	656	7,896.0 (11531.0)	107	25,755.4 (27,166.0)	763	1,008,103.7 (14,368.0)

cSVD: cerebral small vessel disease; WMH: white matter hyperintensities; EPVS: enlarged perivascular spaces; CMB: cerebral microbleed. – is used where data were not available.

5.3.1 Early life factors and cSVD

5.3.1.1 Birth factors and cSVD

Available birth data varied for each cohort. Data on maternal age and birth weight were available for all cohorts. However for STRADL these data were defined as 35 years and below vs older than 35 at the birth of the child (maternal age) and low birth weight (< 5.5 lbs) vs normal birth weight (> 5.5 lbs) rather than on a continuous scale. Data on maternal age is therefore presented separately for STRADL and are not included in the meta-analysis. Data on birth weight in STRADL is not analysed due to the low number of participants with birth weight <5 lbs. Data on birth length and ponderal index were available for the Dutch Famine Birth cohort, the LBC 1936 and Simpson cohort.

Also collected in three cohorts were; whether the participant's mother was married at birth (STRADL, Dutch Famine Birth Cohort, Simpson cohort) and whether the participant was preterm (vs full term; STRADL, LBC 1936 and Simpson cohort). These data could not be analysed for STRADL due to the low number of participants in the unmarried/preterm group (Table 5.1 B).

Maternal age

Maternal age was similar across the Dutch Famine Birth Cohort, the LBC 1936 and the Simpson cohort ($F(2, 365) = 0.58$, $p=0.56$). Mean maternal age was 27.4 (SD 6.1), 28.2 (SD 5.7) 28.0 (SD 6.4) respectively and 27.9 (SD 6.0) overall. In STRADL 10.7% of participants had a mother over the age of 35 at birth.

Maternal age was not associated with cSVD in the meta-analysis of the Dutch Famine Birth cohort, the LBC 1936 and the Simpson cohort. However, in the Dutch famine cohort only, increasing maternal age was associated with increased risk of WMH (per year, OR 1.10, 95% CI 1.01-1.20, $p=0.03$, figure 5.1 A) and in STRADL, having a mother older than 35 at birth was associated with increased risk of one or more cortical infarct (OR 7.80, 95% CI 1.58-40.1, $p=0.01$).

Increasing maternal age was not associated with WMH volume in the LBC 1936 or Simpson cohort (figure 5.2 A).

Birth weight

Birth weight was similar across the Dutch Famine Birth Cohort, the LBC 1936 and the Simpson cohort ($F(2, 365)= 0.99$, $p=0.37$), Mean birth weight was 3417.5g (SD 503.4), 3351.5g (SD 482.1), 3333.6g (SD 457.2) respectively and 3367.3g (SD 481.8) overall. In STRADL 2.4% of participants had low birth weight.

In the meta-analysis of the Dutch Famine Birth cohort, the LBC 1936 and Simpson cohort, increasing birth weight was associated with fewer lacunes (per 100g, OR 0.93 95% CI 0.87-1.00, $p=0.04$, figure 5.1 B). Results from the remaining lesions were in the expected direction (increasing birth weight and lower risk of cSVD) but did not reach statistical significance.

Birth weight was not associated with WMH volume in the LBC 1936 or the Simpson cohort (figure 5.2 B).

Birth length

Birth length was similar across the Dutch Famine Birth Cohort, the LBC 1936 and the Simpson cohort ($F(2, 298)= 2.05$, $p=0.13$). Mean birth length was 51.9cm (SD 8.0), 50.0cm (SD 3.3), 50.7cm (SD 2.8) respectively and 51.0cm (SD 5.6) overall.

Birth length was not associated with cSVD in the meta-analysis of the Dutch Famine Birth cohort, the LBC 1936 and the Simpson cohort. However in individual cohorts, increasing birth length was associated with decreased risk of micro-bleeds (Dutch Famine Birth Cohort only: OR 0.68 0.49-0.94 $p=0.02$) and increased risk of infarcts (LBC 1936 only: OR 1.28, 95% CI 1.01-1.62, $p=0.04$) (figure 5.1 C).

Increasing birth length was not associated with WMH volume in the LBC 1936 or Simpson cohort (figure 5.2 C).

Ponderal index

Ponderal index was different across the Dutch Famine Birth Cohort, the LBC 1936 and the Simpson cohort ($F(2, 297)= 4.72$, $p=0.01$). Mean ponderal index was 26.16 (SD 2.3), 27.33 (SD 5.29) and 25.55 (SD 4.10) respectively and 26.26 (SD 3.96) overall.

Ponderal index was not associated with cSVD in the meta-analysis of the Dutch Famine Birth cohort, the LBC 1936 and the Simpson cohort, however point estimates were in the expected direction for total cSVD burden, WMH burden, lacunes, infarcts

and EPVS (higher ponderal index associated with fewer lesions). In the LBC 1936 increasing ponderal index was associated decreased risk of moderate to severe total cSVD score (OR 0.85, 95% CI 0.74-0.98, p=0.03, figure 5.1 D).

Increasing ponderal index was not associated with WMH volume in LBC 1936 or Simpson cohort (figure 5.2 D).

Mother not married at birth

The percentage of participants whose Mother was not married at the time of their birth varied between cohorts ($\chi^2(3)= 39.1$, $p<0.001$; STRADL 1.2%; Dutch Famine Birth cohort 19.5%; Simpson cohort 10.0%).

Having a mother not married at birth was not associated with any markers of cSVD (figure 5.1 E) or WMH volume in the Simpson cohort (B= 0.46, p=0.40) (WMH volume data not available for the other cohorts).

Preterm

The percentage of participants who were preterm varied between cohorts ($\chi^2(3)= 72.3$, $p<0.001$; STRADL 2.3%; LBC 1936 39.0%; Simpson cohort 12.7%).

Being preterm was not associated with any markers of cSVD (figure 5.1 F) or WMH volume in the LBC 1936 or Simpson cohort (figure 5.2 E).

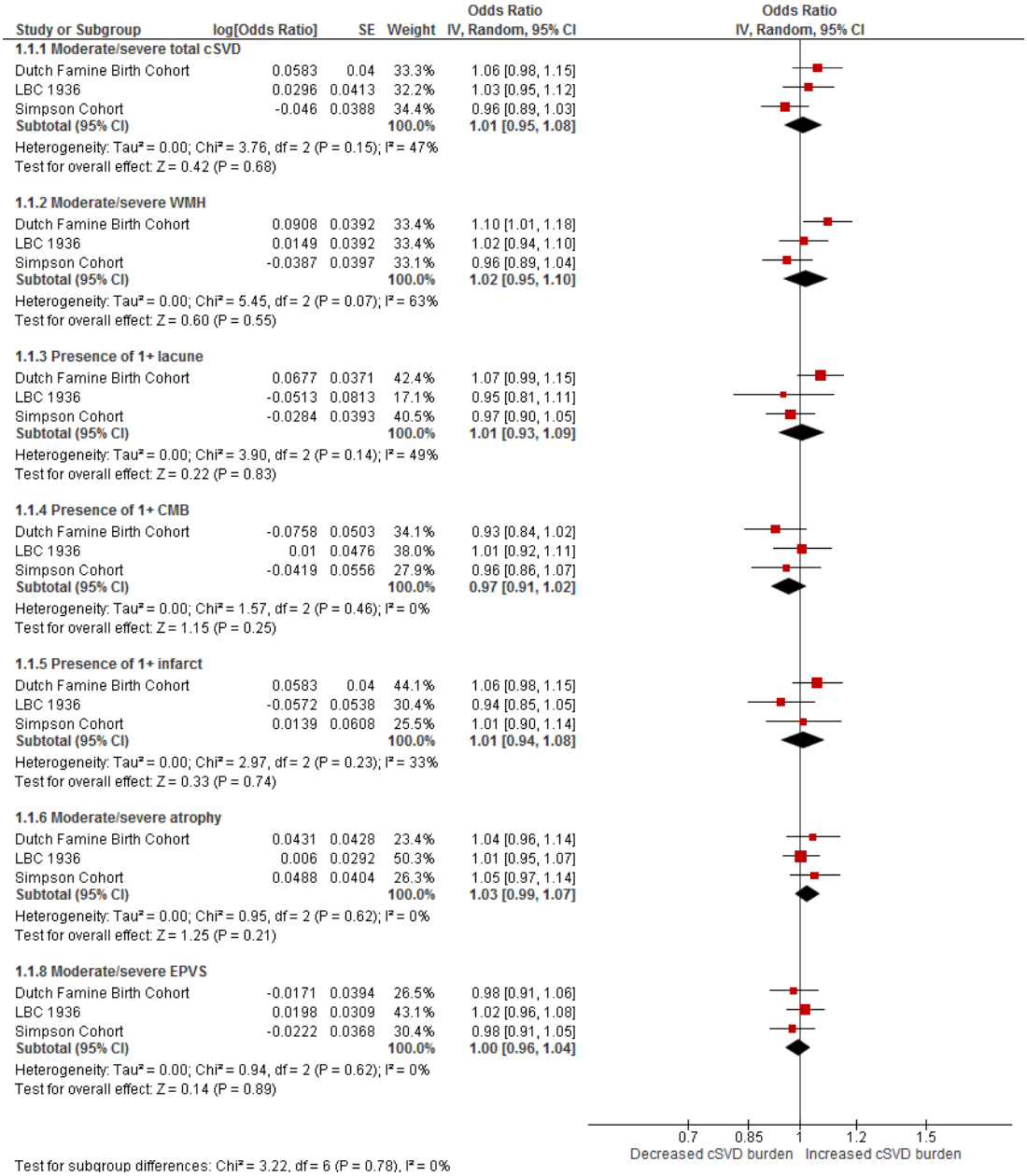
Other birth factors and cSVD in individual cohorts

The Dutch Famine Birth cohort collected several additional birth variables which are shown in table 5.2. Increasing maternal weight before birth was associated with decreased risk of lacunes only (per kg, OR 0.93 95% CI 0.87-0.997, p=0.04); increased head circumference to length ratio was associated with increased risk of micro-bleeds (OR 1.23 95% CI 1.01-1.50, p=0.04) and increased head circumference was associated with increased risk of moderate to severe atrophy (per cm, OR 1.55 95% CI 0.37-2.92, p=0.03). No placental measurements (volume, area and area to birth weight ratio) or famine exposure were associated with total or individual markers of cSVD.

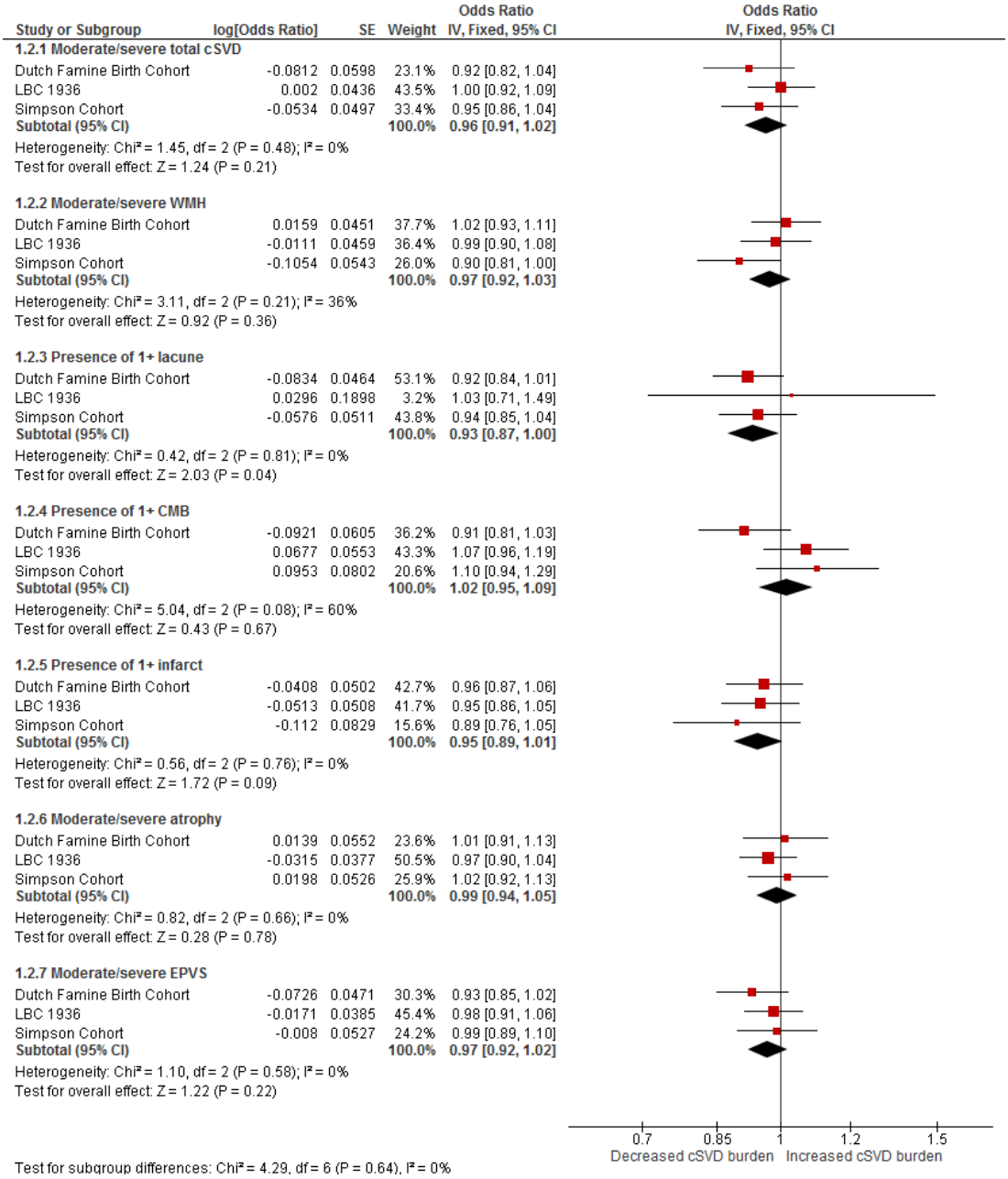
In the Simpson cohort increased placental weight was associated with decreased risk of moderate to severe total cSVD score (per 100g, OR 0.66, 95% CI 0.45-0.96, p=0.03), WMH (OR 0.60, 95% CI 0.38-0.94, p=0.03) and infarcts (OR 0.41, 95% CI 0.20-0.85, p=0.02) and WMH volume (β= -0.26, p=0.02, table 5.2).

Figure 5.1 (A-F) Forest plots showing associations between birth factors common to the Dutch Famine Birth cohort, LBC 1936 and Simpson cohort (A-D), the Dutch Famine Birth Cohort and Simpson cohort (E), the LBC 1936 and Simpson cohort (F)

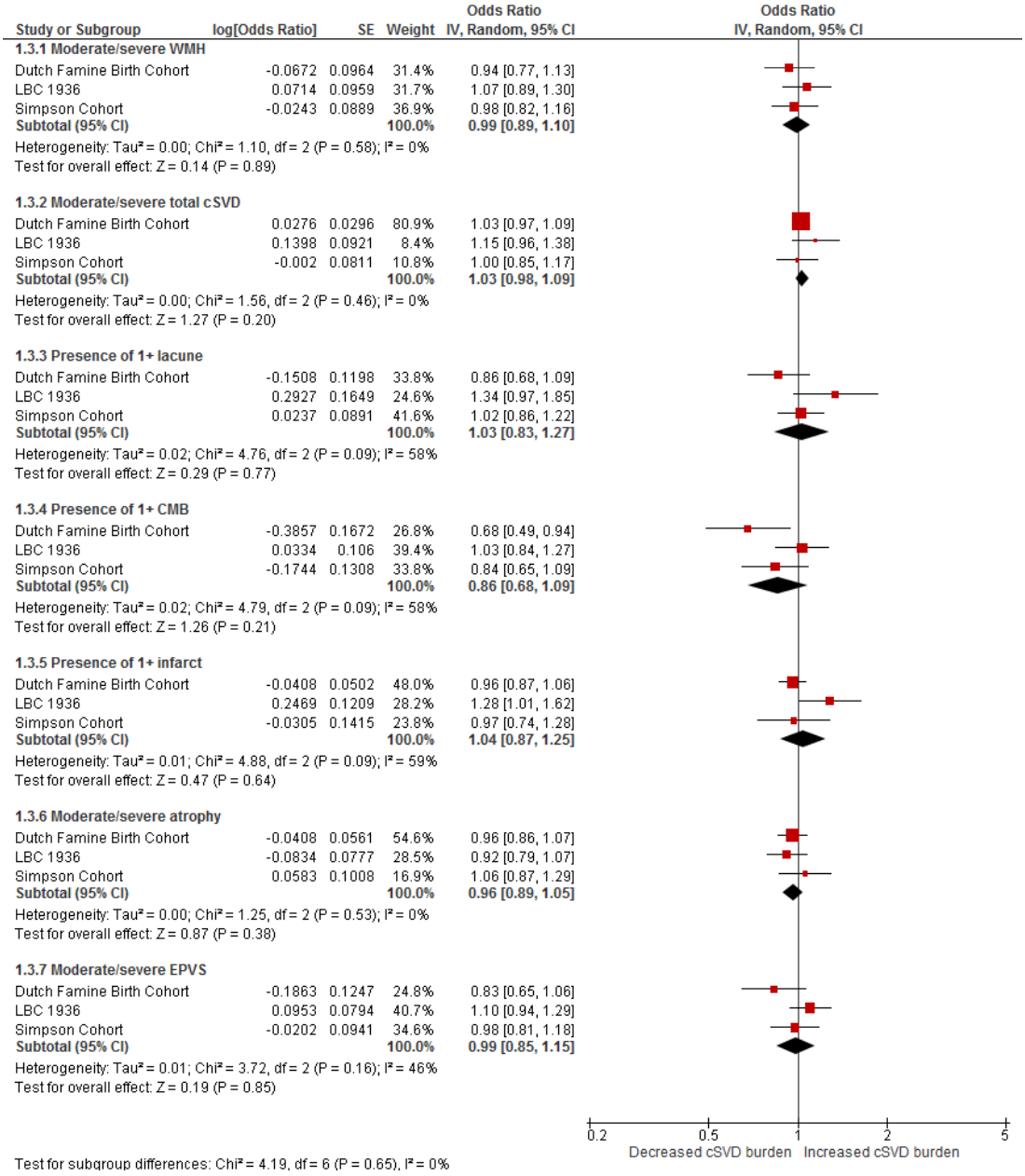
(A) Increasing maternal age



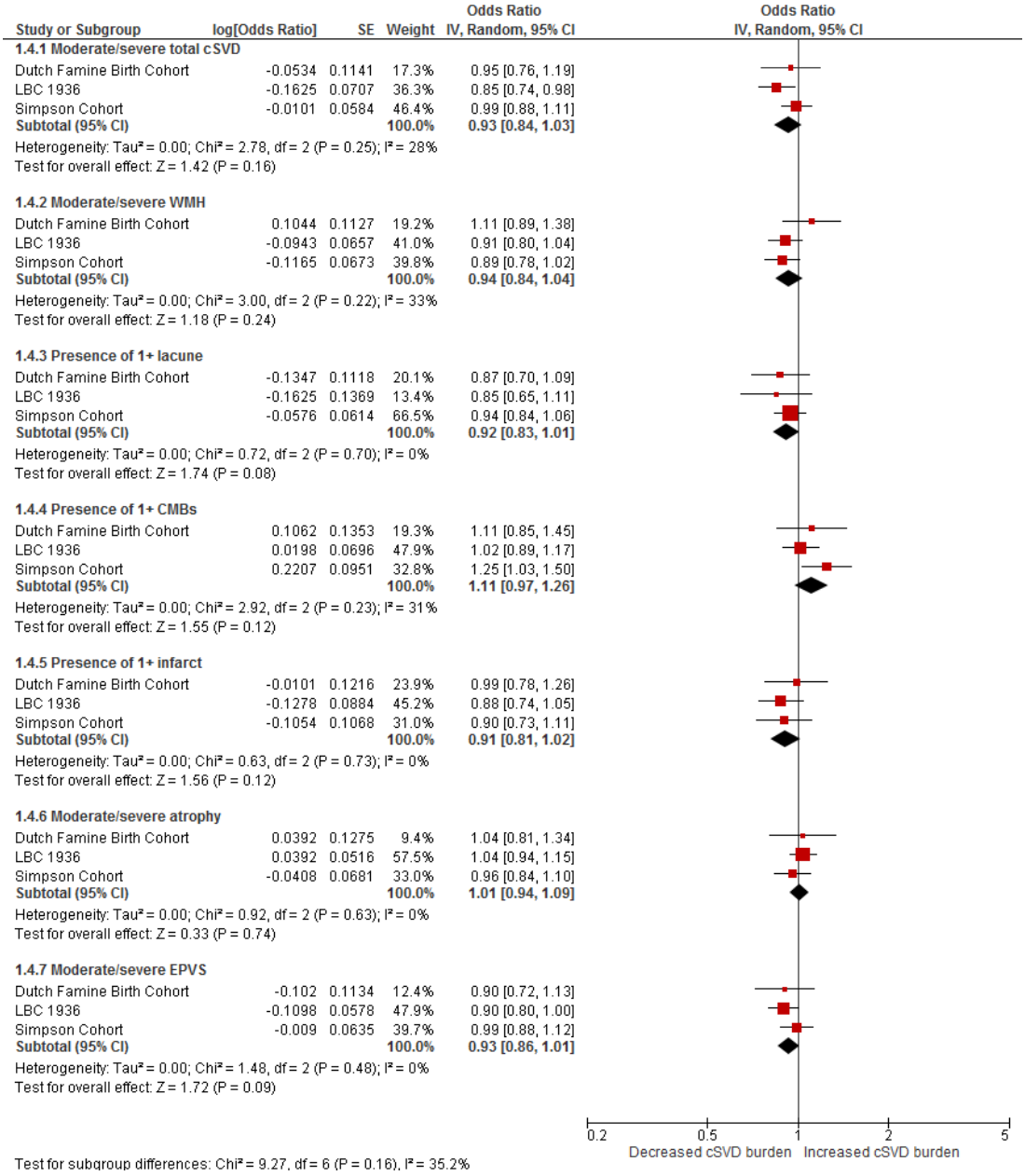
(B) Increasing birth weight



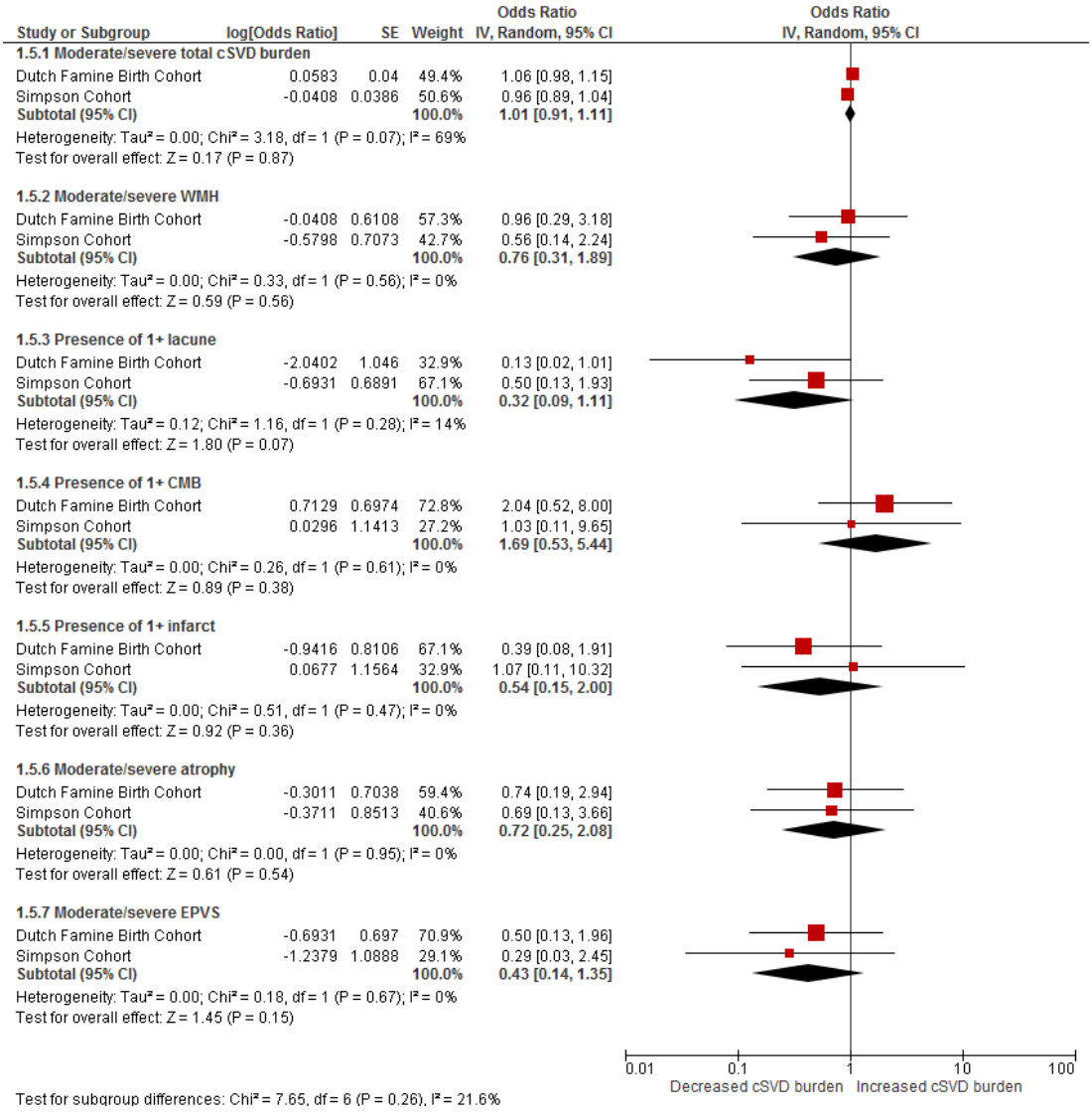
(C) Increasing birth length



(D) Increasing ponderal index



(E) Mother not married at birth



(F) Preterm

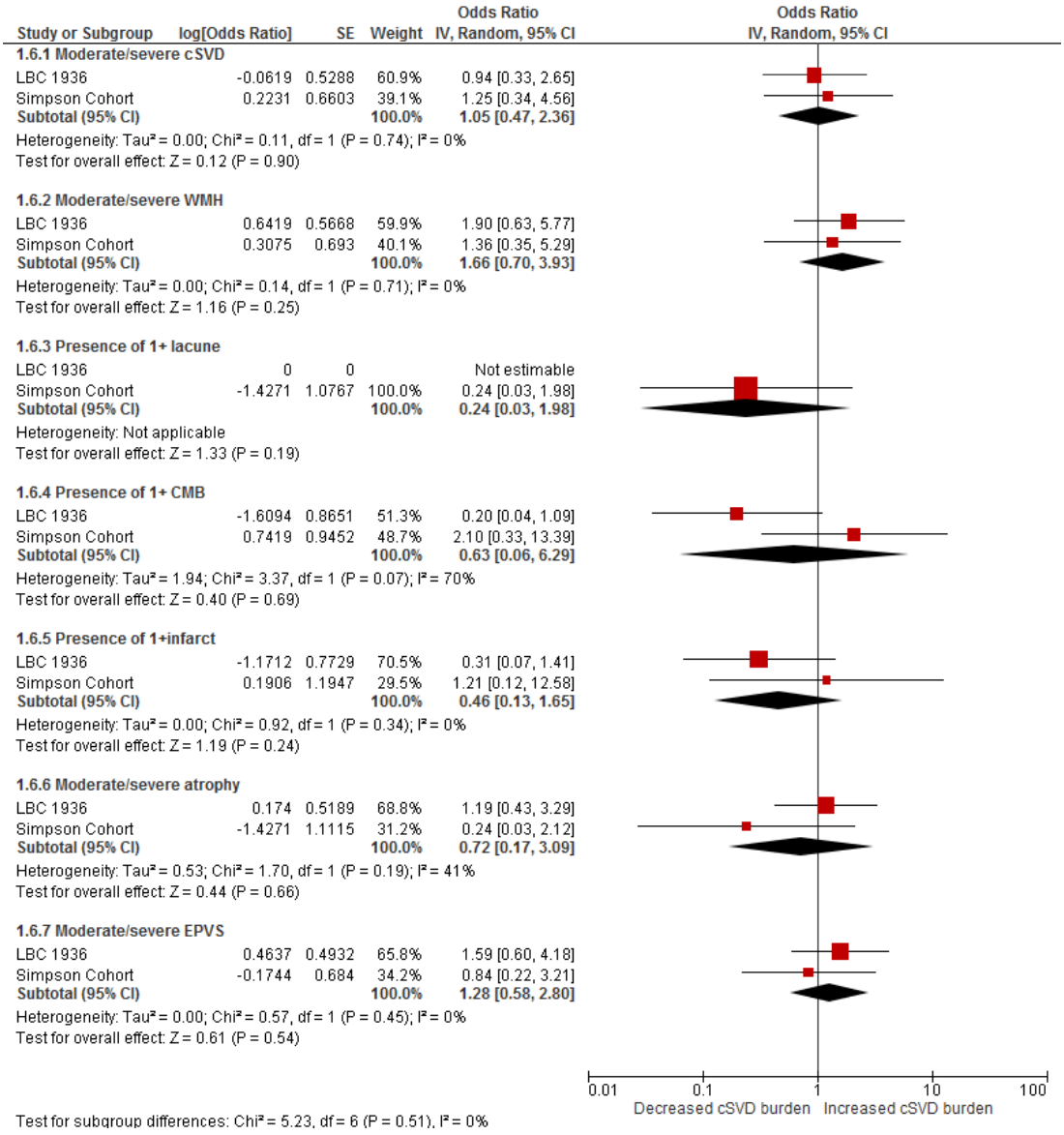
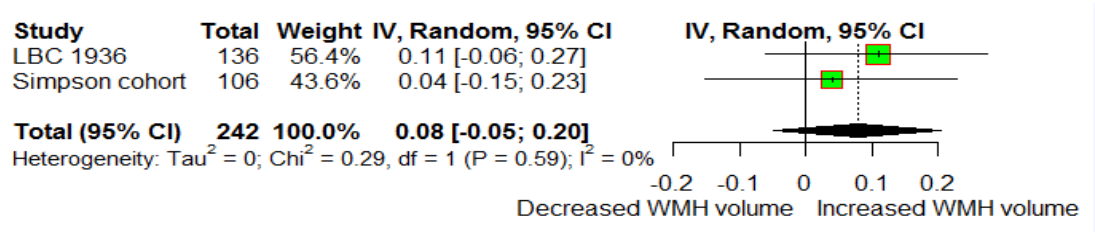
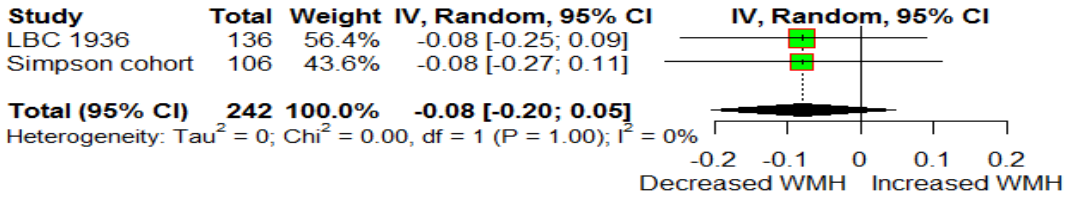


Figure 5.2 (A-F) Forest plots showing associations between birth factors common to the Dutch Famine Birth cohort, LBC 1936 and Simpson cohort (a-d), the Dutch Famine Birth Cohort and Simpson cohort (e), the LBC 1936 and Simpson cohort (f) and features of SVD. All analyses adjusted for age, sex, hypertension, smoking behaviour and adult SES. OR<1: Early life factor decreases risk of SVD feature. OR> 1: Early life factor increases risk of SVD feature

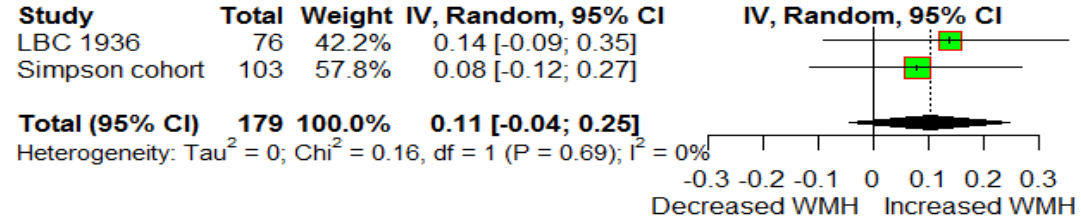
(A) Increasing maternal age



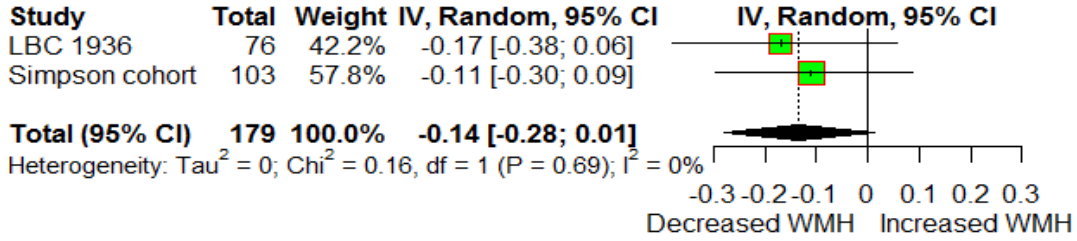
(B) Increasing birth weight



(C) Increasing birth length



(D) Increasing ponderal index



(E) Preterm

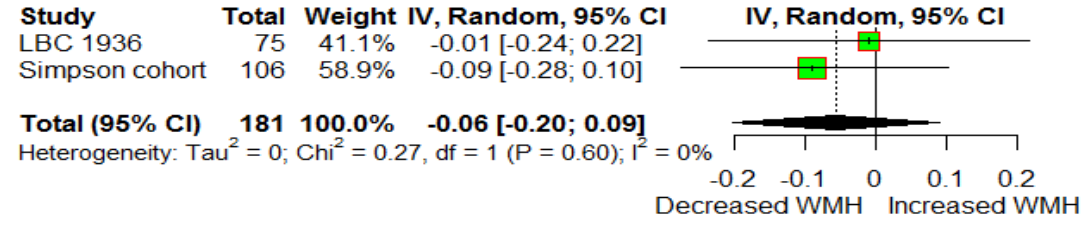


Figure 5.2 (A-E) Forest plots showing associations between birth factors and WMH volume in the LBC 1936 and Simpson cohort.

Table 5.2 Associations between birth factors in STRADL, the Dutch Famine Birth cohort and the Simpson cohort and features of SVD, multiple logistic regression: Odds ratios are presented for A) moderate or severe cSVD compared to none or mild B) moderate or severe WMH compared to none or mild C) presence of one or more lacune compared to D) presence of one or more CMB compared to none E) presence of one or more infarct compared to none F) moderate or severe atrophy compared to none or mild G) none moderate or severe EPVS compared to none or mild H) moderate or severe basal ganglia iron deposits compared to none or mild.

		STRADL		**Dutch famine**		**Simpsons**	
		OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
A	**Moderate or severe total cSVD score**						
	Mother older than 35	0.54 (0.19-1.53)	0.25	-	-	-	-
	Maternal weight	-	-	-	-	-	-
	Head circumference (cm)	-	-	0.97 (0.70-1.41)	0.70	-	-
	Head circumference to length ratio	-	-	1.09 (0.92-1.30)	0.34	-	-
	Head circumference to weight ratio	-	-	1.27 (0.91-1.78)	0.17	-	-
	Placental weight (g)	-	-	-	-	**0.66 (0.45-0.96)**	**0.03**
	Placental volume	-	-	1.00 (0.998- 1.002)	0.68	-	-
	Placental area	-	-	1.001 (0.996-1.01)	0.67	-	-
	Placental area to birth weight ratio	-	-	1.19 (0.95-1.50)	0.14	-	-
	Famine exposure	-	-				

	Born before the famine	-	-	0.15 (0.01-1.45)	0.10	-	-
	Exposed in early gestation	-	-	0.45 (0.1-1.96)	0.29	-	-
	Conceived after the famine	-	-	Reference		-	-
B	**Moderate/severe WMH**						
	Mother older than 35	0.51 (0.11-2.31)	0.38	-	-	-	-
	Maternal weight	-	-			-	-
	Head circumference (cm)	-	-	1.04 (0.74-1.45)	0.82		
	Head circumference to length ratio	-	-	1.04 (0.89-1.23)	0.61	-	-
	Head circumference to weight ratio	-	-	0.96 (0.69-1.34)	0.82	-	-
	Placental weight (g)	-	-	-	-	**0.60 (0.38-0.94)**	**0.03**
	Placental volume	-	-	1.002 (1.00-1.004)	0.09	-	-
	Placental area	-	-	1.001 (0.996-1.01)	0.63	-	-
	Placental to weight ratio	-	-	1.08 (0.87-1.35)	0.50	-	-
	Famine exposure	-	-				
	Born before the famine	-	-	0.79 (0.11-5.80)	0.82	-	-
	Exposed in early gestation	-	-	0.66 (0.17-2.64)	0.56	-	-
	Conceived after the famine	-	-	Reference		-	-
C				**Presence of 1+ lacune**			
	Mother older than 35	0.52 (0.07-4.18)	0.54	-	-	-	-

	Maternal weight	-	-	-	-	-	-
	Head circumference (cm)	-	-	0.83 (0.59-1.16)	0.28	-	-
	Head circumference to length ratio	-	-	0.99 (0.85-1.17)	0.94	-	-
	Head circumference to weight ratio	-	-	1.24 (0.89-1.72)	0.21	-	-
	Placental weight (g)	-	-	-	-	0.79 (0.55-1.15)	0.21
	Placental volume	-	-	1.001 (0.999-1.003)	0.23	-	-
	Placental area	-	-	1.00 (0.995-1.01)	0.99	-	-
	Placental to weight ratio	-	-	1.10 (0.90-1.35)	0.35	-	-
	Famine exposure	-	-				
	Born before the famine	-	-	0.31 (0.03-2.61)	0.28	-	-
	Exposed in early gestation	-	-	1.10 (0.27-4.48)	0.90	-	-
	Conceived after the famine			Reference		-	-
D	**Presence of 1+ cerebral micro-bleed**						
	Mother older than 35	0.38 (0.08-1.74)	0.21			-	-
	Maternal weight	-	-				
	Head circumference (cm)	-	-	1.03 (0.69-1.53)	0.9		
	Head circumference to length ratio	-	-	**1.23 (1.01-1.50)**	**0.04**	-	-

	Head circumference to weight ratio	-	-	1.32 (0.89-1.97)	0.17	-	-
	Placental weight (g)	-	-	-	-	0.89 (0.53-1.49)	0.66
	Placental volume	-	-	0.997 (0.99-1.00)	0.07	-	-
	Placental area	-	-	0.996 (0.988-1.003)	0.26	-	-
	Placental to weight ratio	-	-	0.91 (0.69-1.19)	0.49	-	-
	Famine exposure	-	-				
	Born before the famine	-	-	0.09 (0.003-2.55)	0.16	-	-
	Exposed in early gestation	-	-	0.44 (0.08-2.53)	0.36	-	-
	Conceived after the famine	-	-	Reference		-	-
E	**Presence of 1+ infarct**						
	Mother older than 35	**7.80 (1.58-40.1)**	**0.01**	-	**-**	-	-
	Maternal weight	-	-	-	**-**	-	**-**
	Head circumference (cm)	-	-	0.91 (0.63-1.32)	0.63	-	**-**
	Head circumference to length ratio	-	-	1.01 (0.84-1.57)	0.95	-	-
	Head circumference to weight ratio	-	-	1.20 (0.84-1.71)	0.31	-	-
	Placental weight (g)	-	-	-	-	**0.41 (0.20-0.85)**	**0.02**
	Placental volume	-	-	1.00 (0.98-1.002)	0.71	-	-
	Placental area	-	-	1.001 (0.995-1.01)	0.81	-	-

	Placental to weight ratio	-	-	1.10 (0.88-1.38)	0.41	-	-
	Famine exposure	-	-				
	Born before the famine	-	-	2.91 (0.36-23.34)	0.32	-	-
	Exposed in early gestation	-	-	1.10 (0.23-5.36)	0.91	-	-
	Conceived after the famine	-	-	Reference		-	-
F	**Moderate/severe atrophy**						
	Mother older than 35	0.42 (0.05-3.42)	0.42	-	-	-	-
	Maternal weight	-	-	-	-	-	-
	Head circumference (cm)	-	-	**1.55 (0.37-2.92)**	**0.03**	-	-
	Head circumference to length ratio	-	-	1.17 (0.98-1.41)	0.09	-	-
	Head circumference to weight ratio	-	-	1.04 (0.73-1.49)	0.82	-	-
	Placental weight (g)	-	-	-	-	0.80 (0.52-1.24)	0.31
	Placental volume	-	-	1.002 (1.00-1.004)		-	-
	Placental area	-	-	1.004 (0.998-1.01)	0.22	-	-
	Placental to weight ratio	-	-	1.16 (0.92-1.47)	0.21	-	-
	Famine exposure	-	-				
	Born before the famine	-	-	0.47 (90.05-4.00)	0.49	-	-
	Exposed in early gestation	-	-	0.66 (0.14-3.09)	0.49	-	-

	Conceived after the famine	-	-	Reference		-	-
G	**Moderate/severe EPVS**						
	Mother older than 35	1.19 (0.42-3.37)	0.75			-	-
	Maternal weight	-	-				
	Head circumference (cm)	-	-	0.94 (0.67-1.33)	0.73	-	-
	Head circumference to length ratio	-	-	1.09 (0.92-1.29)	0.31	-	-
	Head circumference to weight ratio	-	-	1.29 (0.93-1.79)	0.14	-	-
	Placental weight (g)	-	-	-	-	0.92 (0.60-1.41)	0.68
	Placental volume	-	-	0.999 (0.997-1.001)	0.29	-	-
	Placental area	-	-	0.998 (0.993-1.004)	0.61	-	-
	Placental to weight ratio	-	-	1.07 (0.85-1.33)	0.58	-	-
	Famine exposure	-	-				
	Born before the famine	-	-	1.37 (0.20-9.29)	0.75	-	-
	Exposed in early gestation	-	-	0.40 (0.09-1.75)	0.22	-	-
	Conceived after the famine	-	-	Reference		-	-

5.3.1.2 Childhood factors and cSVD

Data on childhood factors differed between cohorts. Education level (low vs high) and parental occupation (manual vs non manual) were available for all cohorts. Childhood and premorbid IQ and mean years of education were available for STRADL, the LBC 1936 and the Simpson cohort. Educational attainment (no qualifications vs O level and above) were available for STRADL and the LBC 1936. The LBC 1936 and Simpson cohort also collected several additional proxy measures of childhood SES.

Childhood and premorbid IQ

Childhood IQ score was similar across STRADL, the LBC 1936 and the Simpson cohort ($F(2)= 1.35$, $p= 0.26$, table 5.1).

Across the three cohorts, increasing childhood IQ was associated with decreased risk of moderate or severe WMH (per IQ point, OR 0.99 95% CI 0.98-1.00, p=0.03), lacunes (OR 0.98 95% CI 0.97-0.99, p=0.04), infarcts (OR 0.98 95% CI 0.97-1.00, p=0.03) and total cSVD burden (OR 0.98 95% CI 0.96-1.00, p=0.04). In STRADL only, increasing childhood IQ was associated with fewer micro-bleeds (OR 0.95, 95% CI 0.91-0.99, p=0.02) (figure 5.3 A).

The LBC 1936 had higher NART scores (higher premorbid IQ) than the Simpson cohort ($F(1)= 28.91$, $p<0.001$). Mean NART score was 34.43 (SD 8.13) in the LBC 1936 and 30.0 (SD 7.92) in the Simpson cohort. Premorbid IQ was measured differently in STRADL and so differences in scores could not be directly compared with the other cohorts.

Across the three cohorts increasing premorbid IQ was associated with decreased risk of infarcts (per point, OR 0.97 95% CI 0.94-0.99, p=0.007).

Childhood and premorbid IQ were not associated with WMH volume in the LBC 1936 and Simpson cohort (figure 5.4 A-B).

Education

The percentage of participants with low education level (≤ 11 years: STRADL, LBC 1936 and Simpson cohort; lower secondary school and above: Dutch Famine Birth cohort) were similar between the cohorts ($\chi^2(3)= 8.0$, $p=0.05$; STRADL 61.7%; Dutch Famine 62.7%,; LBC 1936 71.7%; Simpson cohort 80.9%; overall 53.6%).

Across all cohorts low education was associated with increased risk of micro-bleeds. (vs high education level, OR 1.78 95% CI 1.04-3.04, p=0.04, figure 5.3 C).

Across STRADL, LBC 1936 and the Simpson cohort increasing mean years of education was associated with lower risk of infarcts (per year, OR 0.97 95% CI 0.95-1.00, p= 0.02), more atrophy (per year, OR 1.17 95% CI 1.04-1.31, p=0.01) and more lacunes (OR 1.37 95 % CI 1.07-1.76, p=0.01) (figure 5.3 D). Mean years of education was not available for the Dutch Famine Birth cohort.

Having no qualifications was associated with increased risk of micro-bleeds (vs O level and above, OR 1.88 95% CI 1.11-3.19, p=0.02) in STRADL and the LBC 1936 (figure 5.3 E).

Education level and mean years of education were not associated with WMH volume in the LBC 1936 and Simpson cohort (figure 5.4 C-D).

Childhood SES

The percentage of participants with manual parental occupation were similar between cohorts ($\chi^2(3)= 5.7$, p=0.13; STRADL 67.9%, Dutch famine birth cohort, 66.7%; LBC 1936, 74.2%; Simpson cohort, 69.1%; overall 73.5%).

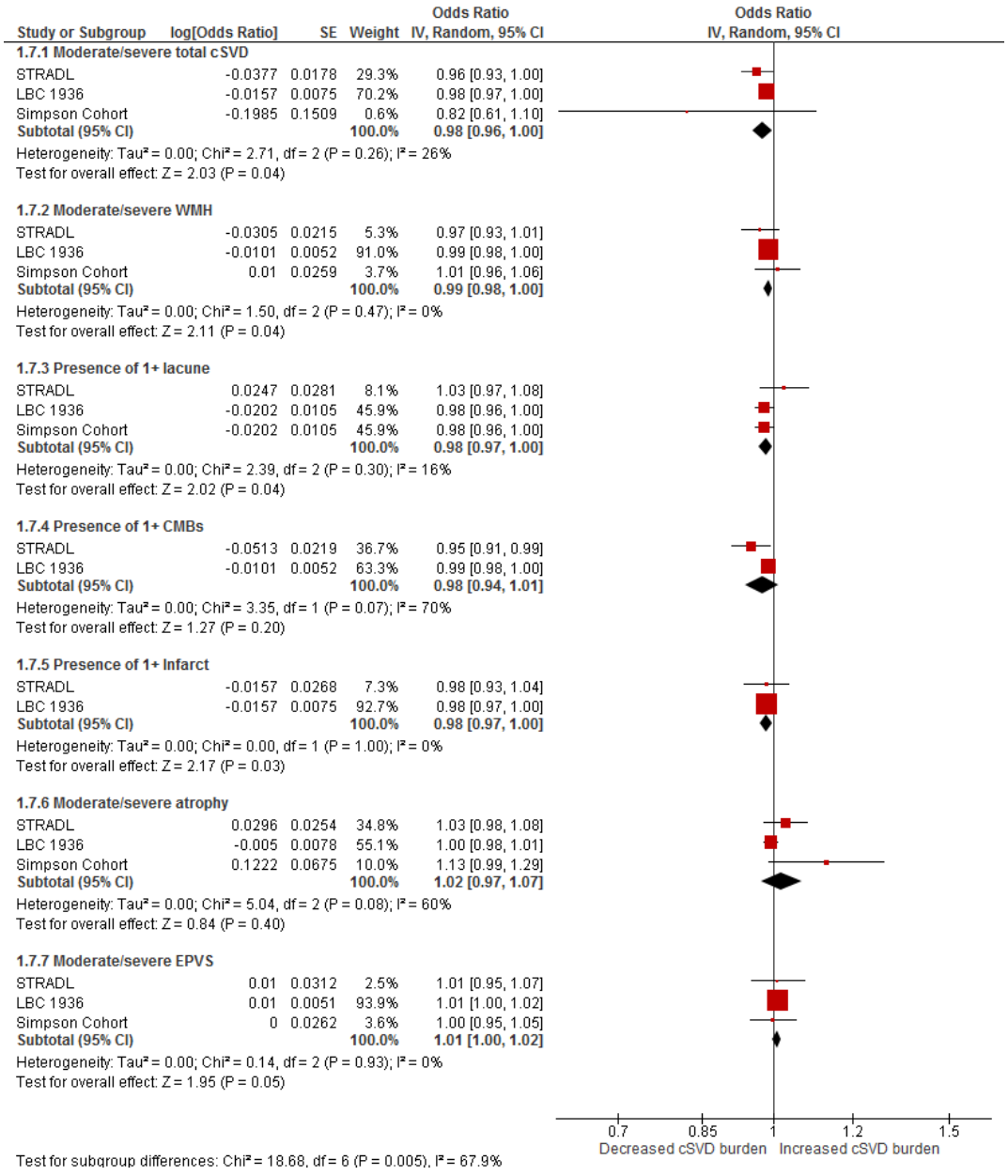
Manual father's occupation was not associated with cSVD in the meta-analysis. In individual cohorts manual father's occupation was associated with decreased risk of cSVD (vs non-manual, Simpsons cohort: OR 0.36 95% CI 0.14-0.93, p=0.03) and decreased lacunes (LBC 1936: OR 0.39 95% CI 0.17-0.89, p=0.03) (figure 5.3 F).

Having an outdoor (vs indoor) toilet and increasing number of people sharing a toilet were associated with increased risk of infarcts (Simpson cohort: OR 13.31, 95% CI 1.52-116.56, p= 0.02, figure 5.3 G; OR 1.18, 95% CI 1.001-1.39, p=0.049, figure 5.3 H). Increasing overcrowding index was associated with decreased EPVS (Simpson cohort OR 0.39, 95% CI 0.20-0.76, p=0.01, figure 5.3 I).

Manual parental occupation, having an outdoor toilet, number of people sharing a toilet and overcrowding index were not associate with WMH volume in the LBC 1936 or Simpson cohort (figure 5.4 E-H).

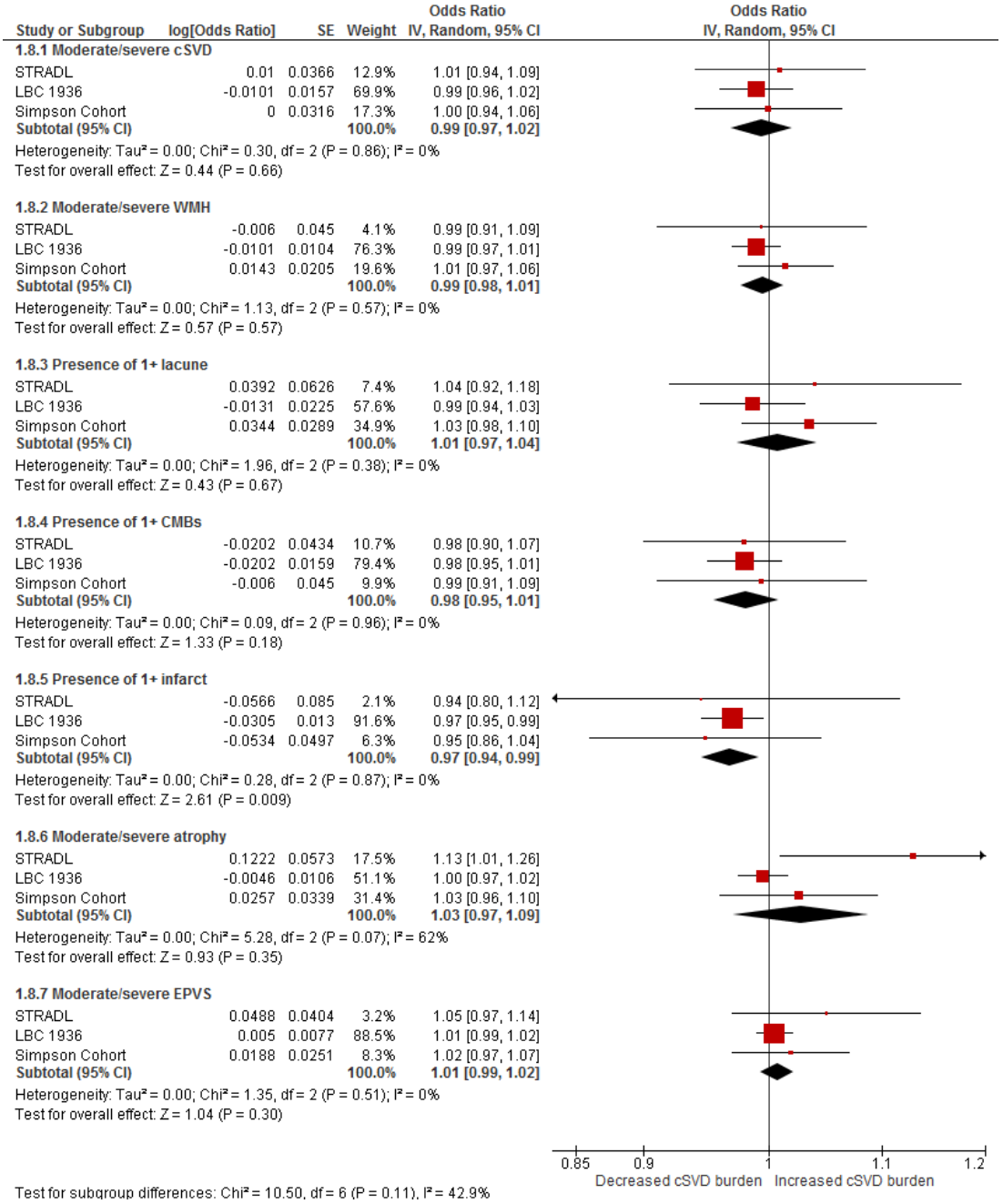
Figure 5.3 (A-I) Forest plots showing associations between (a) childhood IQ (b) premorbid IQ (c) education level (d) mean years of education (e) no qualifications (f) manual parental occupation (g) outdoor toilet (h) increasing number of people sharing a toilet (i) overcrowding index and features of cSVD. All analyses adjusted for age, sex, hypertension, smoking behaviour and adult SES. OR<1: Early life factor decreases risk of SVD feature. OR> 1: Early life factor increases risk of cSVD features

(A) Childhood IQ

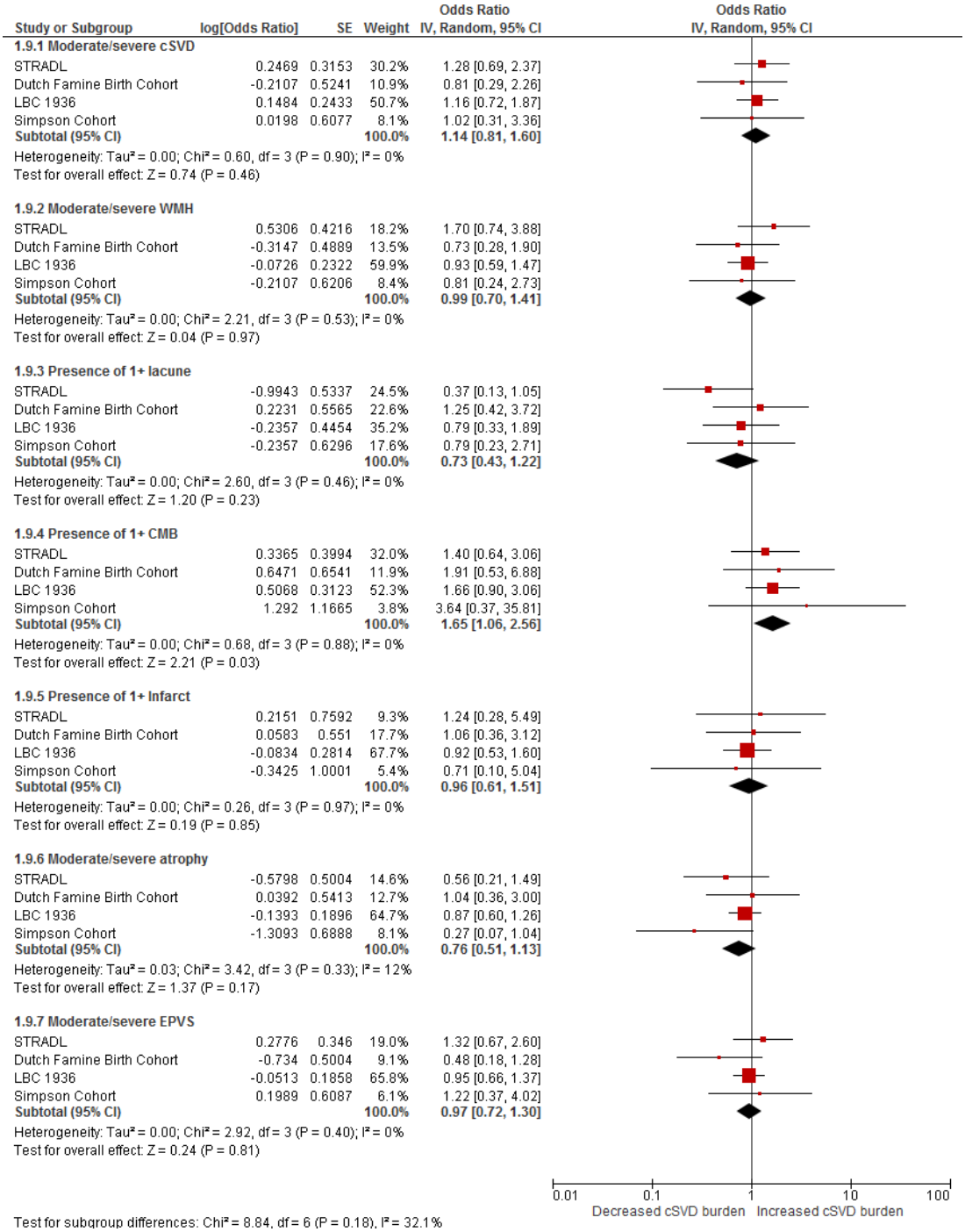


Note: Simpson cohort not included in some analysis due to low sample size. Those analyses including Simpson cohort adjusted for age and sex only.

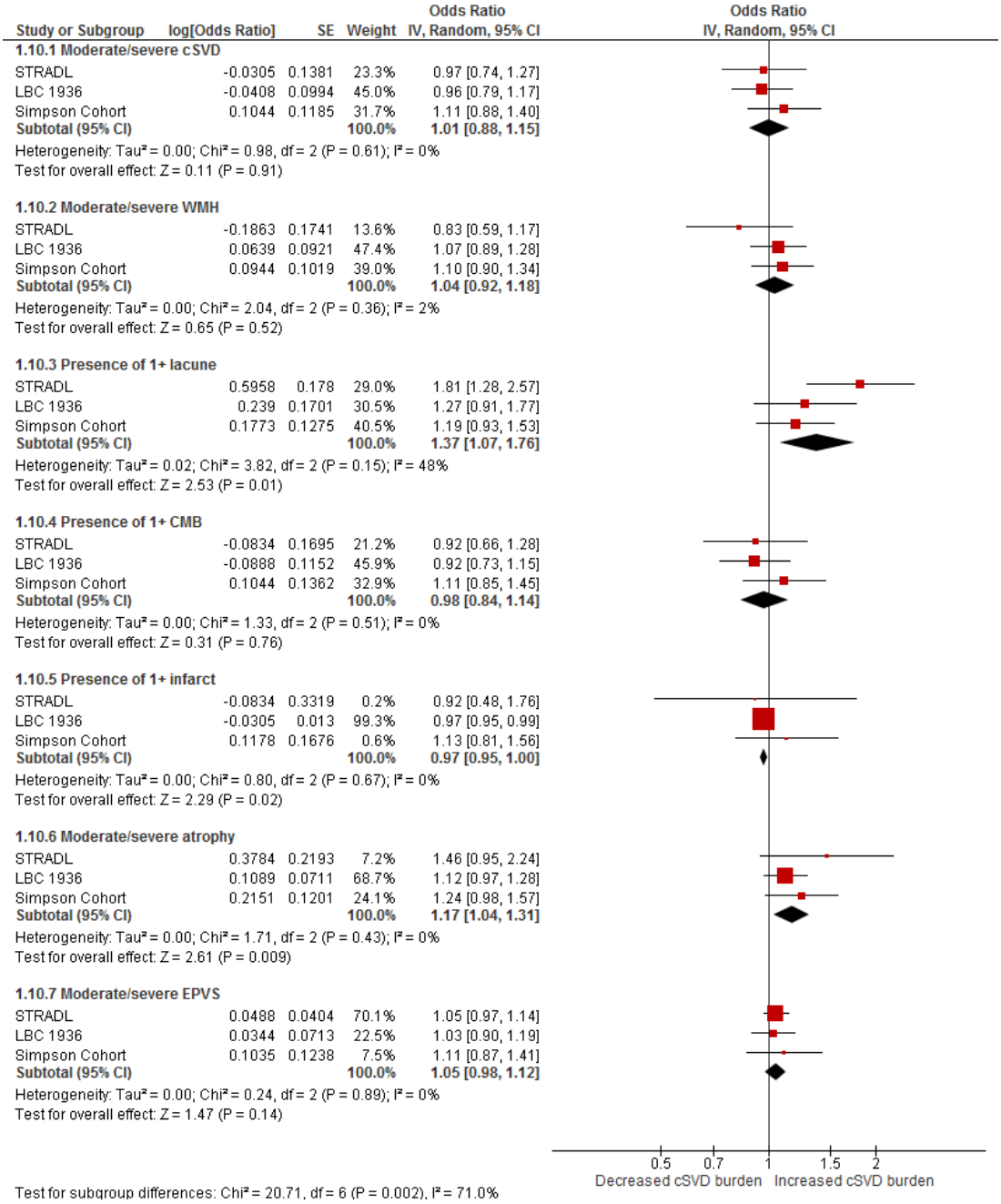
(B) Premorbid IQ



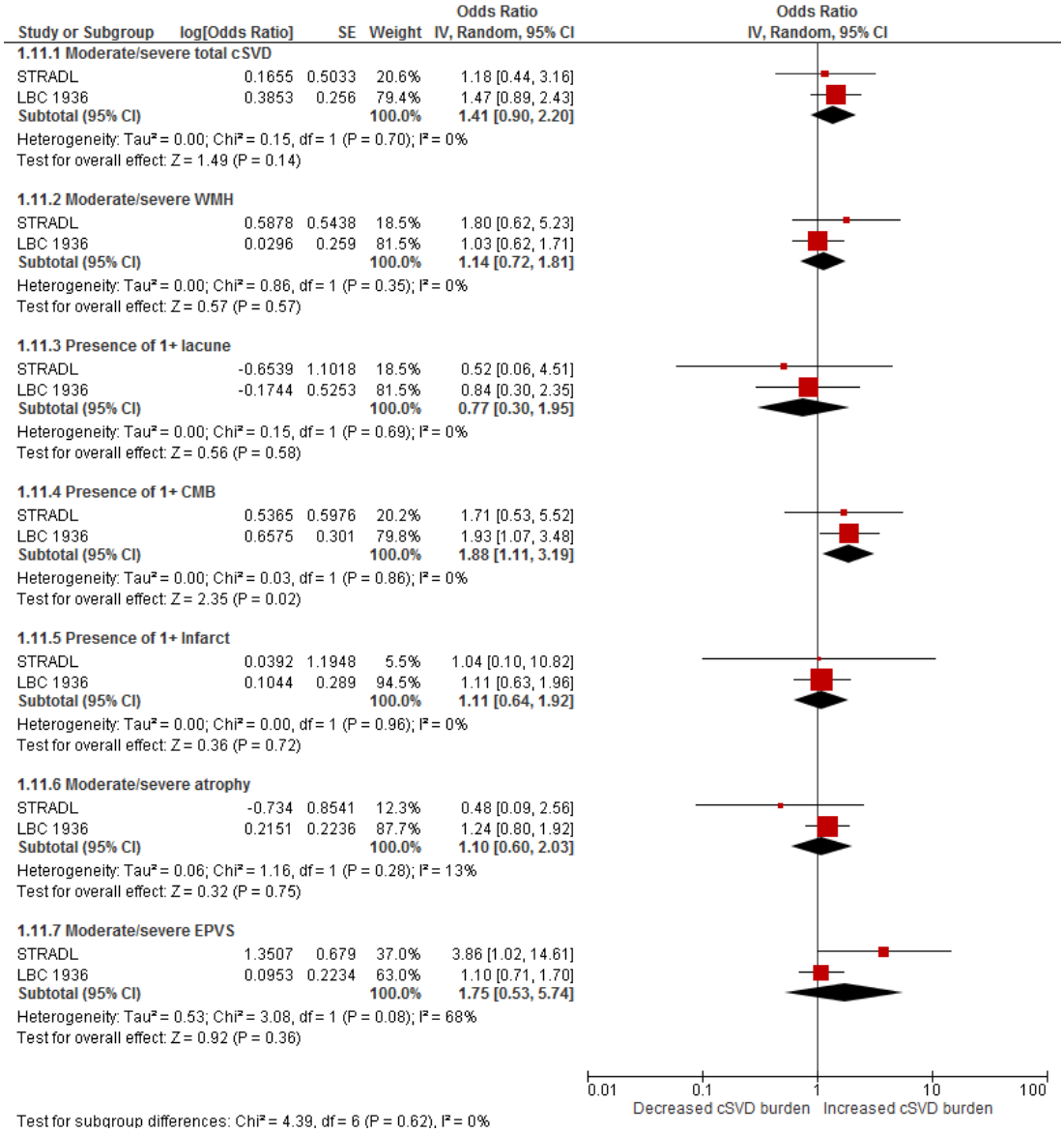
(C) Low education



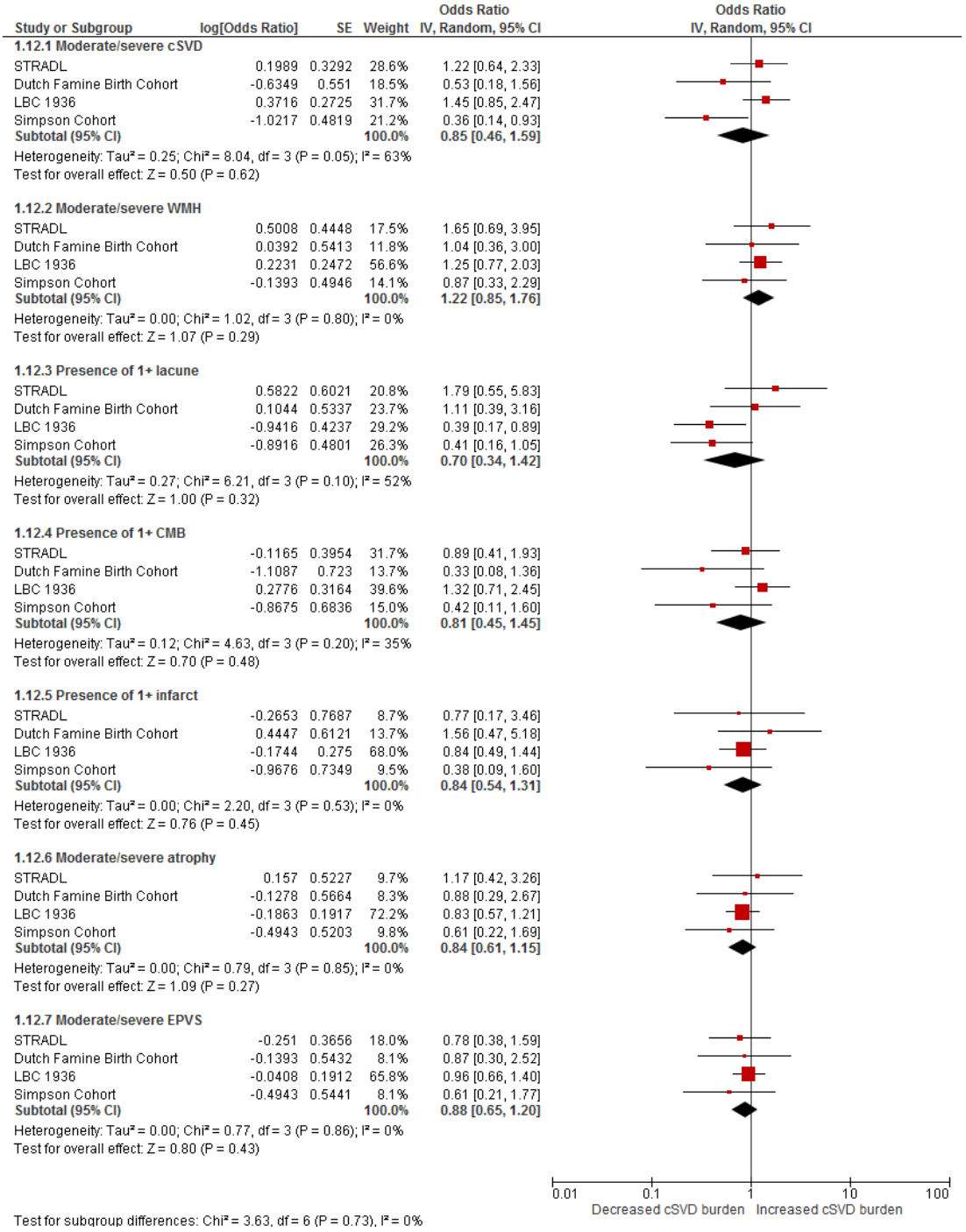
(D) Mean years of education



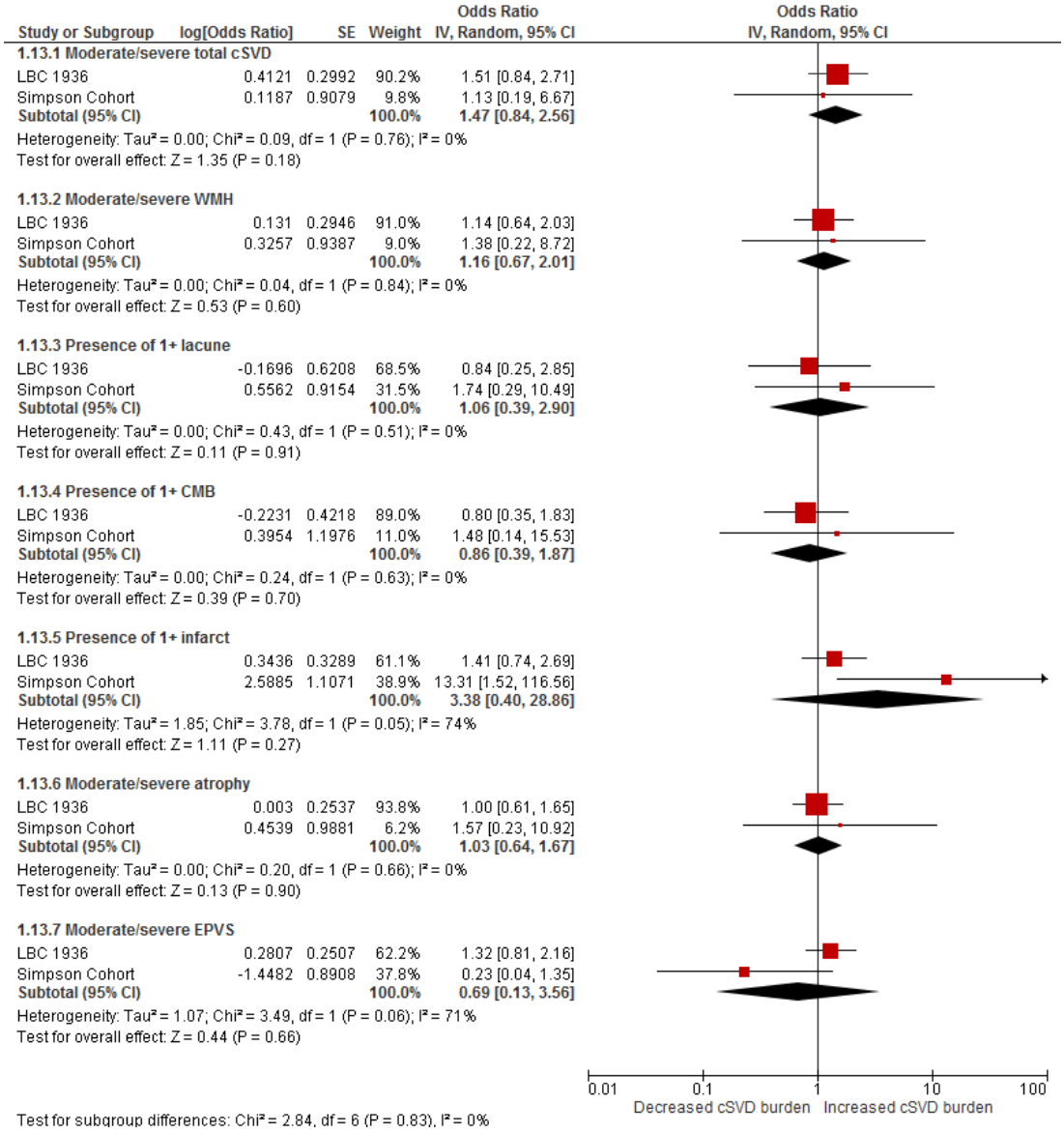
(E) No qualifications



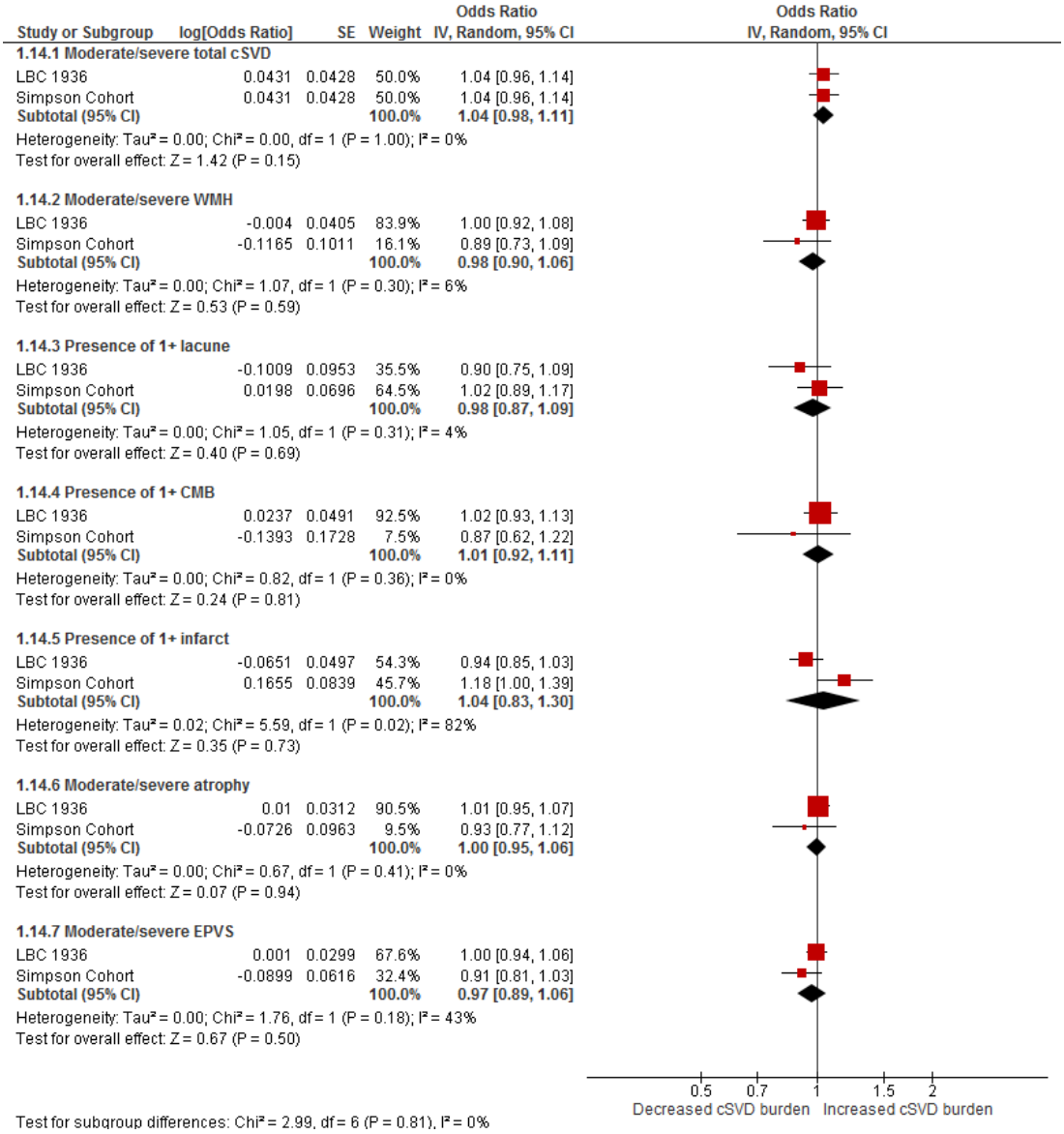
(F) Manual paternal occupation



(G) Outdoor toilet



(H) Increasing number of people sharing a toilet



(I) Overcrowding index

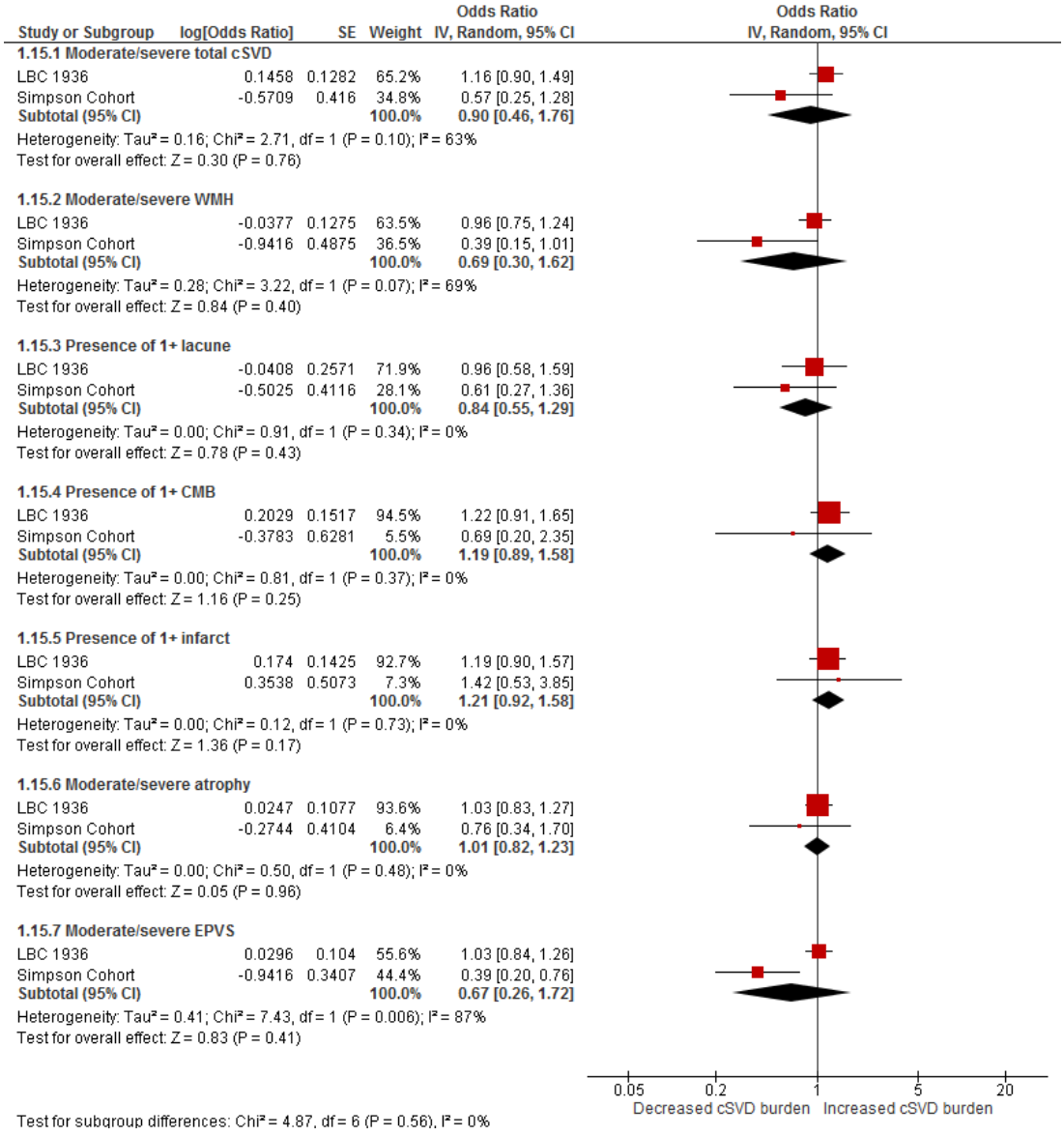
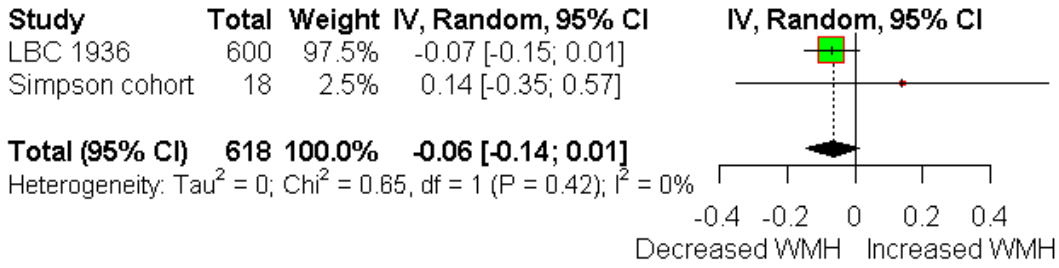


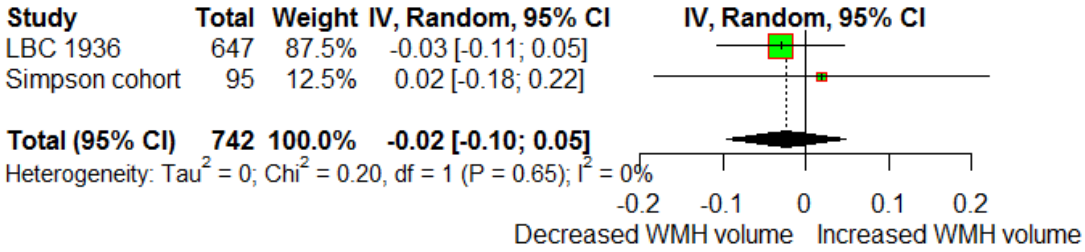
Figure 5.3 (A-I) Forest plots showing associations between (a) childhood IQ (b) premorbid IQ (c) education level (d) mean years of education (e) no qualifications (f) manual parental occupation (g) outdoor toilet (h) increasing number of people sharing a toilet (i) overcrowding index and features of cSVD. All analyses adjusted for age, sex, hypertension, smoking behaviour and adult SES. OR<1: Early life factor decreases risk of SVD feature. OR> 1: Early life factor increases risk of cSVD features

Figure 5.4 (A-H) Forest plots showing associations between birth factors and WMH volume in the LBC 1936 and Simpson cohort. All analyses adjusted for age, sex, hypertension, smoking behaviour and adult SES

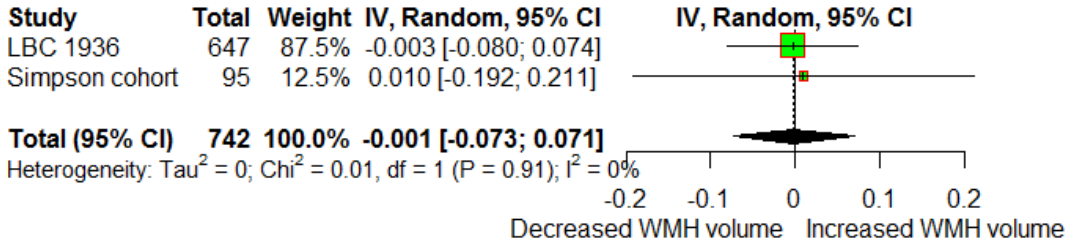
(A) Childhood IQ



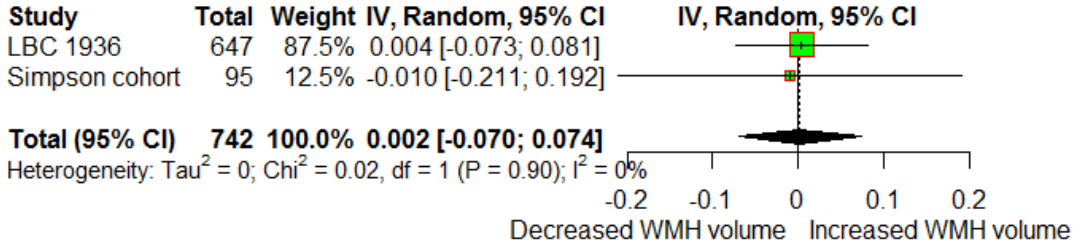
(B) Premorbid IQ



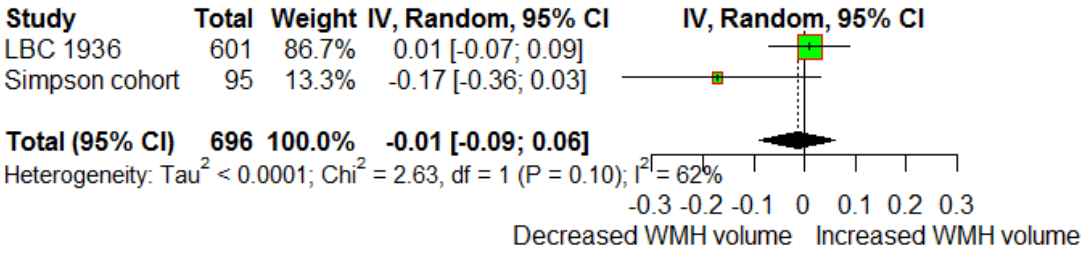
(C) Mean years of education



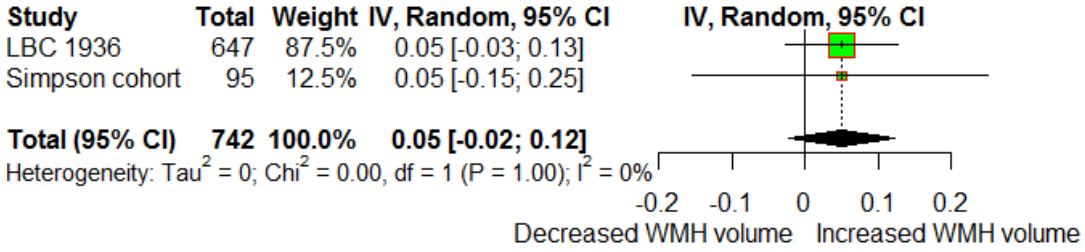
(D) Low education



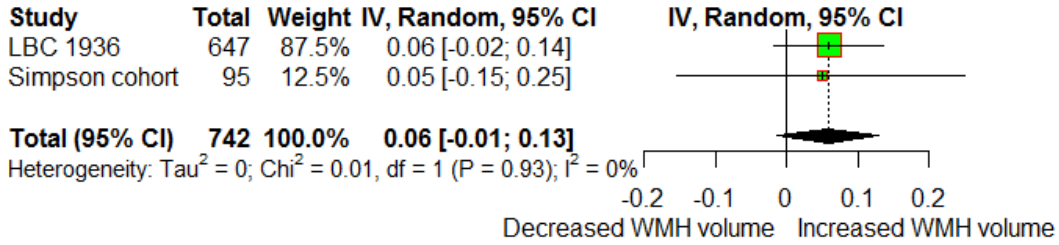
(E) Manual paternal occupation



(F) Outdoor toilet



(G) Number of people sharing a toilet



(H) Overcrowding index

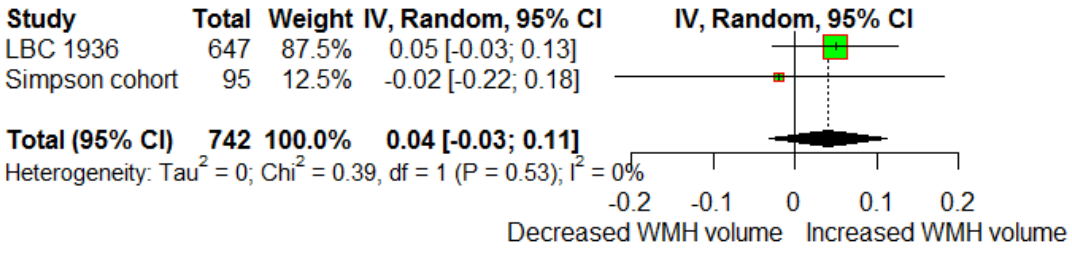


Figure 5.4 (A-H) Forest plots showing associations between birth factors and WMH volume in the LBC 1936 and Simpson cohort. All analyses adjusted for age, sex, hypertension, smoking behaviour and adult SES

5.3.1.3 Multiple regression analysis adjusting for other early life factors

To assess the independence of associations between ponderal index/childhood/premorbid IQ, education and childhood SES, multiple regression analyses were performed adjusting for other early life factors in addition to vascular risk factors and SES in adulthood.

In the LBC 1936 the association between ponderal index and total cSVD was attenuated after adjustment for education level and parental occupation (OR 0.88 95% CI 0.76-1.02, p=0.08, table 5.3)

Across STRADL and the LBC 1936 all associations between childhood IQ and cSVD were attenuated after adjustment for other early life factors. Associations between childhood IQ and total cSVD burden (OR 0.98, 0.97-0.997, p=0.02) and infarcts (OR 0.98, 0.97-1.00, p=0.04, table 5.4 A) remained statistically significant after adjustment for education and parental occupation. It was not possible to include the Simpson cohort in this analysis due to the small number of participants with childhood IQ scores.

Across the LBC 1936 and Simpson cohort the association between premorbid IQ and infarcts remained statistically significant after adjustment for education and parental occupation (OR 0.96, 0.93-0.99, p=0.01, Table 5.4 B).

Table 5.3: Multiple regression analysis of early life factors and cSVD in the Dutch Famine Birth Cohort, the LBC 1936 and the Simpson cohort.

All analyses are adjusted for each early life factor in the table and age, sex, hypertension, smoking behaviour and adult SES

	Dutch Famine Cohort		LBC 1936		Simpson cohort		Meta-analysis	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Moderate/severe cSVD								
Ponderal index	0.89 (0.70-1.14)	0.37	0.88 (0.76-1.02)	0.08	0.997 (0.89-1.11)	0.95	0.94 (0.87-1.03)	0.18
Low education	0.72 (0.23-2.30)	0.58	0.19 (0.03-1.41)	0.11	1.20 (0.36-4.05)	0.77	0.71 (0.30-1.67)	0.43
Manual Father's occupation	0.59 (0.19-1.87)	0.58	0.66 (0.11-3.89)	0.64	**0.33 (0.13-0.89)**	**0.03**	**0.44 (0.23-0.87)**	**0.02**
Moderate/severe WMH								
Ponderal index	1.07 (0.85-1.34)	0.56	0.93 (0.81-1.07)	0.29	0.94 (0.83-1.06)	0.28	1.04 (0.84-1.30)	0.71
Low education	0.56 (0.19-1.65)	0.29	0.27 (0.04-1.71)	0.16	0.77 (0.22-2.64)	0.67	0.56 (0.26-1.19)	0.13
Manual Father's occupation	1.12 (0.37-3.32)	0.84	1.10 (0.17-7.20)	0.92	0.79 (0.29-.16)	0.64	0.95 (0.47-1.89)	0.88
Presence of 1+ lacune								
Ponderal index	0.92 (0.74-1.16)	0.49	NA	NA	0.96 (0.86-1.08)	0.52	0.95 (0.86-1.05)	0.32
Low education	1.42 (0.47-4.29)	0.53	NA	NA	0.79 (0.22-2.85)	0.71	1.10 (0.48-2.55)	0.82
Manual Father's occupation	1.01 (0.50-2.95)	0.98	NA	NA	**0.34 (0.13-0.90)**	**0.03**	0.62 (0.21-1.78)	0.37

Presence of 1+ CMB								
Ponderal index	1.02 (0.77-1.37)	0.87	NA	NA	**1.26 (1.03-1.55)**	**0.03**	1.16 (0.95-1.42)	0.15
Low education	1.34 (0.26-6.89)	0.73	NA	NA	3.50 (0.35-34.72)	0.29	1.85 (0.49-7.04)	0.37
Manual Father's occupation	0.31 (0.07-1.28)	0.31	NA	NA	0.34 (0.08-1.53)	0.16	**0.33 (0.12-0.92)**	**0.03**
Presence of 1+ infarct								
Ponderal index	0.88 (0.69-1.12)	0.29	0.91 (0.77-1.06)	0.22	0.95 (0.78-1.17)	0.64	0.90 (0.71-1.14)	0.37
Low education	1.19 (0.34-4.18)	0.78	0.34 (0.02-5.26)	0.44	0.46 (0.06-3.44)	0.45	0.81 (0.30-.20)	0.68
Manual Father's occupation	1.50 (0.43-5.18)	0.52	0.29 (0.03-2.62)	0.27	0.23 (0.04-1.14)	0.07	0.55 (0.18-1.63)	0.28
Moderate/severe atrophy								
Ponderal index	0.94 (0.73-1.21)	0.61	1.05 (0.95-1.17)	0.31	0.97 (0.86-1.10)	0.68	1.01 (0.94-1.09)	0.80
Low education	1.05 (0.31-3.54)	0.93	1.25 (0.19-8.26)	0.82	0.33 (0.09-1.25)	0.10	0.70 (0.31-1.58)	0.39
Manual Father's occupation	0.83 (0.26-2.69)	0.76	0.69 (0.14-3.49)	0.69	0.75 (0.26-2.18)	0.59	0.77 (0.38-1.55)	0.46
Moderate/severe EPVS								
Ponderal index	0.83 (0.65-1.06)	0.14	0.93 (0.83-1.04)	0.18	1.02 (0.90-1.14)	0.78	0.95 (0.87-1.04)	0.29
Low education	0.35 (0.11-1.10)	0.07	0.29 (0.05-1.72)	0.17	1.09 (0.31-3.87)	0.90	0.51 (0.23-1.15)	0.11
Manual Father's occupation	0.79 (0.26-2.42)	0.68	1.25 (0.25-6.33)	0.79	0.48 (0.16-1.50)	0.21	0.70 (0.35-1.42)	0.33

cSVD= cerebral small vessel disease; WMH= white matter hyperintensities; CMB= cerebral microbleed; EPVS= enlarged perivascular spaces

NA: due to the small sample size and low number of lacunes and micro-bleeds it was not possible to conduct all analyses. Data on ponderal index were not available for STRADL.

Table 5.4 A-B: Multiple regression analysis of a) Childhood IQ, education, childhood SES and cSVD in STRADL and the LBC 1936 and b) Premorbid IQ, education, childhood SES and cSVD in STRADL, the LBC 1936 and the Simpson cohort

All analyses are adjusted for each early life factor in the table and age, sex, hypertension, smoking behaviour and adult SES.

(A)

	STRADL		LBC 1936		Meta-analysis	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Moderate/severe cSVD						
Childhood IQ	0.97 (0.93-1.004)	0.06	0.99 (0.97-1.00)	0.07	**0.98 (0.97-0.997)**	**0.02**
Low education	0.87 (0.42-1.80)	0.71	0.99 (0.56-1.75)	0.97	0.94 (0.60-1.48)	0.80
Manual Father's occupation	1.11 (0.54-2.28)	0.78	1.32 (0.75-2.32)	0.34	1.24 (0.79-1.93)	0.35
Moderate/severe WMH						
Childhood IQ	0.98 (0.94-1.02)	0.34	0.99 (0.98-1.01)	0.29	0.99 (0.98-1.00)	0.20
Low education	1.19 (0.46-3.06)	0.72	0.79 (0.47-1.33)	0.37	0.87 (0.55-1.37)	0.54
Manual Father's occupation	1.28 (0.51-3.21)	0.60	1.25 (0.75-2.08)	0.39	1.26 (0.80-1.96)	0.32
Presence of 1+ lacune						
Childhood IQ	1.02 (0.95-1.09)	0.66	0.97 (0.95-1.00)	0.04	0.98 (0.95-1.02)	0.29
Low education	0.34 (0.10-1.16)	0.08	1.10 (0.38-3.18)	0.86	0.64 (0.20-2.01)	0.44
Manual Father's occupation	2.74 (0.79-9.50)	0.11	**0.30 (0.13-0.71)**	**0.01**	0.87 (0.10-7.48)	0.90
Presence of 1+ CMB						

Childhood IQ	0.95 (0.90-0.995)	0.03	0.995 (0.98-1.01)	0.59	0.98 (0.93-1.02)	0.32
Low education	1.06 (0.42-2.67)	0.91	1.35 (0.67-2.71)	0.41	1.24 (0.71-2.18)	0.45
Manual Father's occupation	0.78 (0.33-1.87)	0.58	1.20 (0.62-2.31)	0.58	1.02 (0.61-1.73)	0.93
Presence of 1+ infarct						
Childhood IQ	0.98 (0.89-1.08)	0.68	**0.98 (0.97-1.00)**	**0.03**	**0.98 (0.97-0.997)**	**0.02**
Low education	1.14 (0.20-6.50)	0.88	1.07 (0.56-2.05)	0.84	0.95 (0.60-1.48)	0.80
Manual Father's occupation	0.67 (0.13-3.45)	0.63	0.77 (0.43-1.38)	0.38	1.24 (0.79-1.93)	0.35
Moderate/severe atrophy						
Childhood IQ	1.04 (0.98-1.10)	0.24	0.98 (0.99-1.01)	0.67	1.01 (0.96-1.05)	0.79
Low education	0.60 (0.19-1.87)	0.37	0.89 (0.57-1.35)	0.58	0.82 (0.55-1.23)	0.34
Manual Father's occupation	2.12 (0.67-6.68)	0.20	0.88 (0.59-1.31)	0.51	1.13 (0.48-2.64)	0.78
Moderate/severe EPVS						
Childhood IQ	0.98 (0.94-1.02)	0.37	1.01 (0.99-1.02)	0.48	1.00 (0.98-1.02)	0.85
Low education	1.29 (0.58-2.90)	0.53	0.91 (0.59-1.38)	0.65	0.99 (0.67-1.44)	0.94
Manual Father's occupation	0.82 (0.38-1.78)	0.62	1.04 (0.69-1.55)	0.86	0.99 (0.69-1.42)	0.94

(B)

	STRADL		LBC 1936		Simpson cohort		Meta-analysis	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Moderate/severe cSVD								
Premorbid IQ	0.999 (0.93-1.08)	0.98	0.995 (0.97-1.03)	0.74	1.01 (0.95-1.08)	0.75	1.00 (0.98-1.02)	0.82
Low education	1.16 (0.59-2.27)	0.67	0.91 (0.51-1.62)	0.74	1.14 (0.31-4.22)	0.85	1.02 (0.67-1.55)	0.92
Manual Father's occupation	1.20 (0.60-2.40)	0.61	1.42 (0.81-2.46)	0.22	4.93 (0.58-41.59)	0.14	1.40 (0.91-2.14)	0.12
Moderate/severe WMH								
Premorbid IQ	1.01 (0.91-1.11)	0.92	0.99 (0.96-1.02)	0.60	0.98 (0.92-1.05)	0.59	0.99 (0.96-1.02)	0.43
Low education	1.45 (0.60-3.54)	0.41	0.82 (0.48-1.38)	0.45	0.67(0.17-2.60)	0.56	0.92 (0.60-1.42)	0.71
Manual Father's occupation	1.40 (0.56-3.51)	0.48	1.31 (0.79-2.16)	0.29	2.42 (0.47-12.60)	0.29	1.39 (0.90-2.13)	0.14
Presence of 1+ lacune								
Premorbid IQ	1.03 (0.91-1.17)	0.59	0.97 (0.92-1.02)	0.23	1.04 (0.97-1.12)	0.23	1.00 (0.95-1.06)	0.90
Low education	**0.31 (0.10-0.95)**	**0.04**	1.20 (0.40-3.59)	0.74	1.12(0.28-4.41)	0.88	0.72 (0.29-1.79)	0.49
Manual Father's occupation	3.00 (0.85-10.58)	0.09	**0.34 0.14- 0.80)**	**0.01**	2.04 (0.40-10.42)	0.39	1.18 (0.26-5.36)	0.83

Presence of 1+ CMB								
Premorbid IQ	0.95 (0.96-1.02)	0.32	0.99 (0.96-1.03)	0.61	1.02 (0.91-1.13)	0.78	0.99 (0.96-1.02)	0.42
Low education	1.48 (0.87-2.53)	0.38	1.36 (0.67-2.77)	0.39	4.40 (0.38-50.43)	0.23	1.48 (0.87-2.53)	0.15
Manual Father's occupation	0.91 (0.50-1.64)	0.66	1.17 (0.62-2.77)	0.64	0.47 (0.07-2.81)	0.40	0.91 (0.50-1.64)	0.74
Presence of 1+ infarct								
Premorbid IQ	0.98 (0.81-1.18)	0.79	**0.96 (0.93-0.99)**	**0.01**	0.94 (0.85-1.04)	0.22	**0.96 (0.93-0.99)**	**0.01**
Low education	1.29 (0.25-6.67)	0.76	0.97 (0.50-1.87)	0.93	0.39 (0.04-3.48)	0.40	0.95 (0.52-1.71)	0.86
Manual Father's occupation	0.70 (0.14-3.54)	0.67	0.76 (0.43-1.33)	0.33	2.22 (0.15-33.87)	0.57	0.76 (0.46-1.33)	0.37
Moderate/severe atrophy								
Premorbid IQ	1.12 (0.99-1.26)	0.07	0.99 (0.97-1.02)	0.58	1.001 (0.93-1.08)	0.98	1.01 (0.96-1.06)	0.71
Low education	0.45 (0.15-1.35)	0.15	0.86 (0.56-1.31)	0.47	0.28 (0.07-1.12)	0.07	0.61 (0.32-1.16)	0.13
Manual Father's occupation	1.02 (0.58-1.77)	0.16	0.84 (0.57-1.25)	0.39	0.87 (0.21-3.72)	0.86	1.02 (0.58-1.77)	0.95
Moderate/severe EPVS								
Premorbid IQ	1.05 (0.99-1.03)	0.21	1.004 (0.98-1.03)	0.75	1.04 (0.97-1.11)	0.30	1.01 (0.99-1.03)	0.33
Low education	1.45 (0.69-3.05)	0.33	0.97 (0.63-1.48)	0.88	1.62 (0.43-6.03)	0.48	1.11 (0.77-1.59)	0.58
Manual Father's occupation	0.72 (0.33-1.55)	0.40	0.99 (0.67-1.47)	0.96	1.55 (0.40-6.00)	0.53	0.96 (0.68-1.34)	0.80

5.3.2 Early life factors and brain volumes in the LBC and Simpson cohort

Data on brain volumes were only available for the LBC 1936 and Simpson cohort. Total brain volume as a percentage of ICV which was used to indicate global brain atrophy and was calculated in both cohorts. Total brain volume corrected for ICV and ICV were also available for both cohorts. Regional brain volumes collected were different for each cohort.

5.3.2.1 Birth factors and brain volumes

Associations between birth factors and total and regional brain volumes are presented in figure 5.5 A-E and Table 5.5.

Total brain volumes

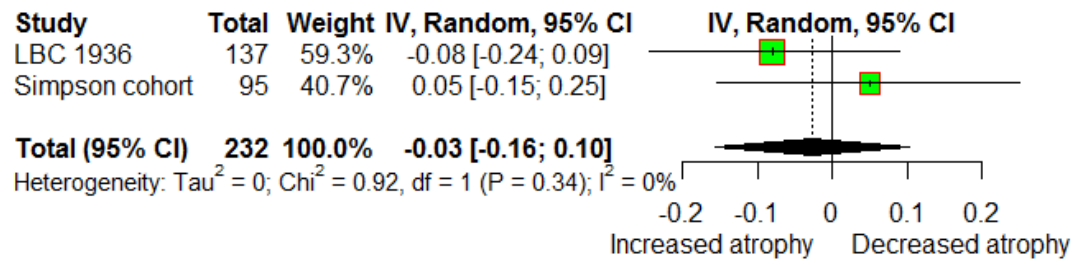
Maternal age, birth length, ponderal index and being preterm were not associated with any brain volume measurements in the LBC 1936 or Simpson cohort (figure 5.5 A, C, D, E).

Across both cohorts increasing birth weight was associated with increased ICV (β= 0.21, p= 0.001, figure 5.5 B iii). In the Simpson cohort only increasing placental weight was associated with increased ICV (β= 0.20, p=0.04).

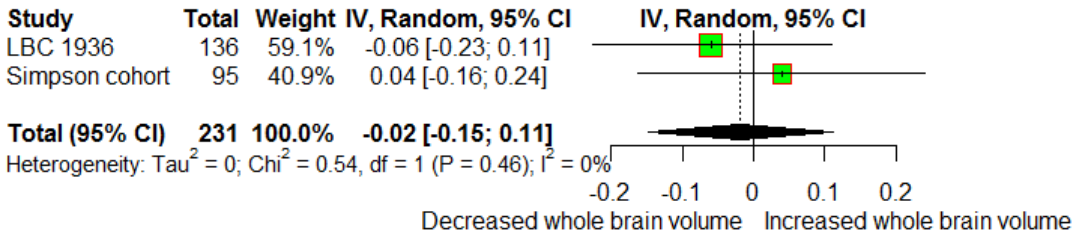
Figure 5.5 A-E: Meta-analysis of birth factors and brain volumes the LBC 1936 and Simpson cohort. Forest plots are presented for (A i-iii) increasing maternal age (B i-iii) increasing birth weight (C i-iii) increasing birth length (D i-iii) increasing ponderal index (E i-iii) preterm. All analyses are adjusted for age, sex, hypertension, smoking behaviour and adult SES. Analyses of birth weight, length and ponderal index are also adjusted for gestational age.

(A) Increasing maternal age

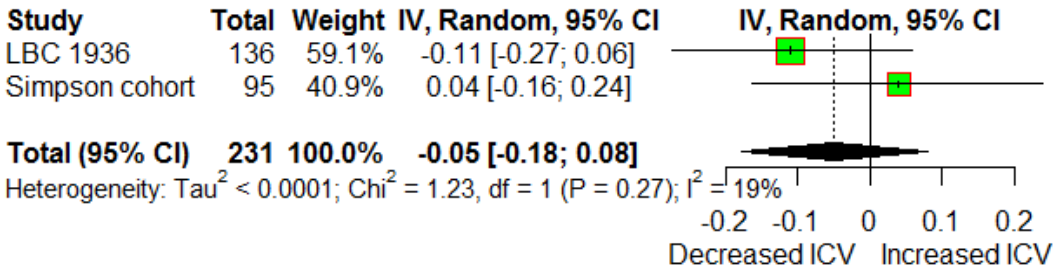
(i) Increasing maternal age and global brain atrophy



(ii) Increasing maternal age and whole brain volume

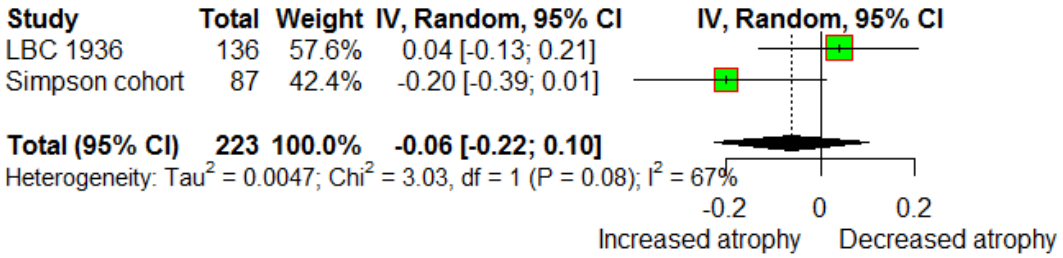


(iii) Increasing maternal age and ICV

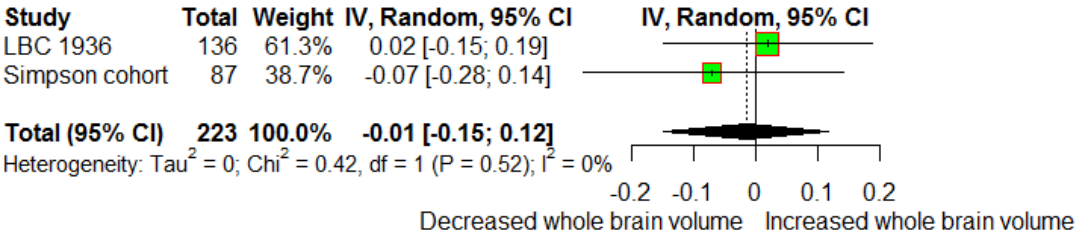


(B) Increasing birth weight

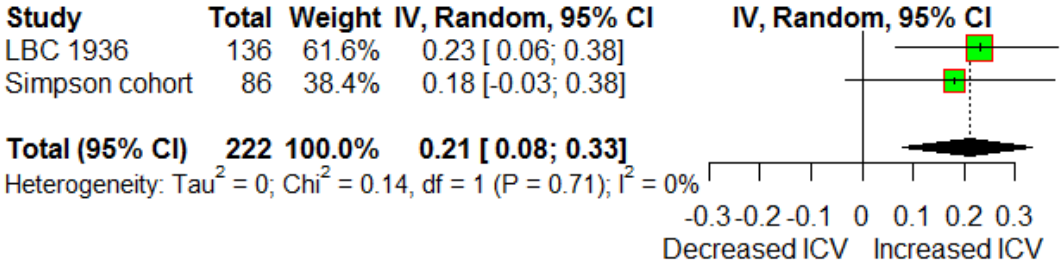
(i) Increasing birth weight and global brain atrophy



(ii) Increasing birth weight and whole brain volume

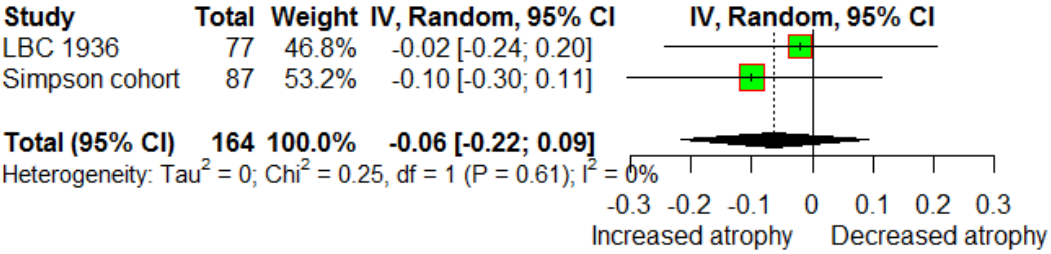


(iii) Increasing birth weight and ICV

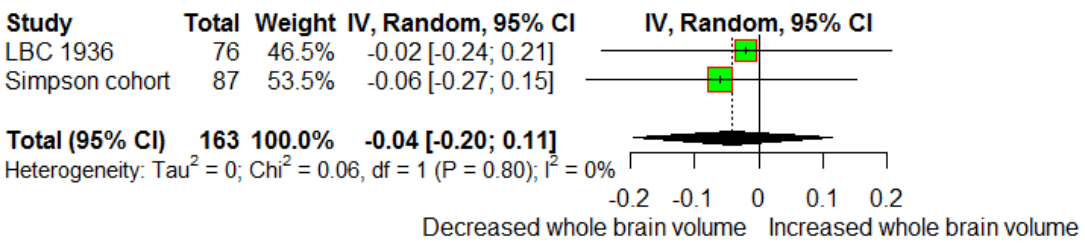


(C) Increasing birth length

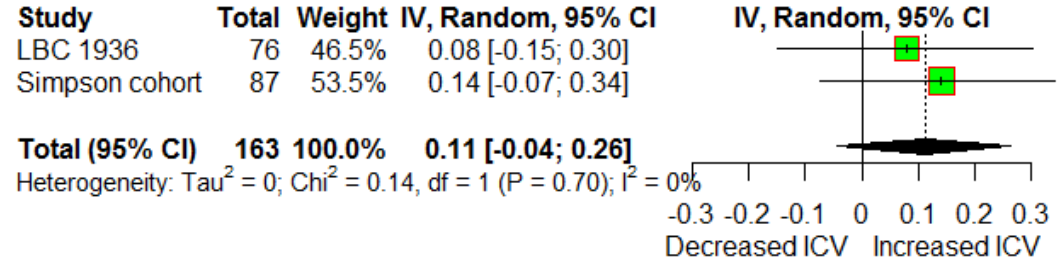
(i) Increasing birth length and global brain atrophy



(ii) Increasing birth length and whole brain volume

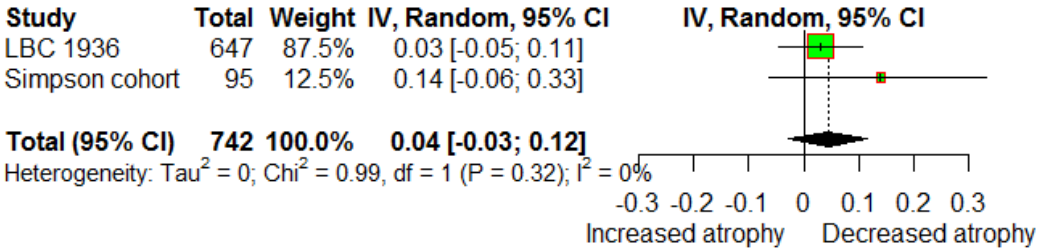


(iii) Increasing birth length and ICV

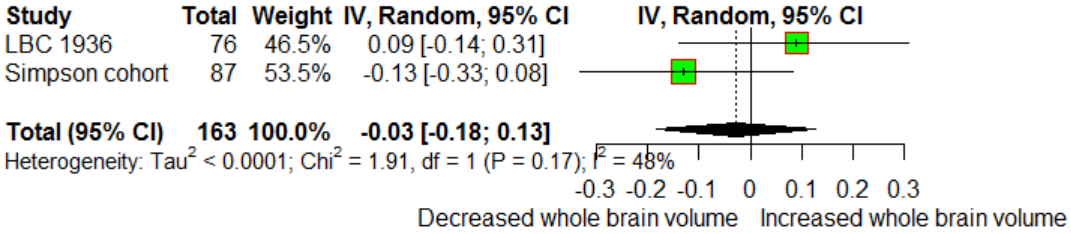


(D) Increasing ponderal index

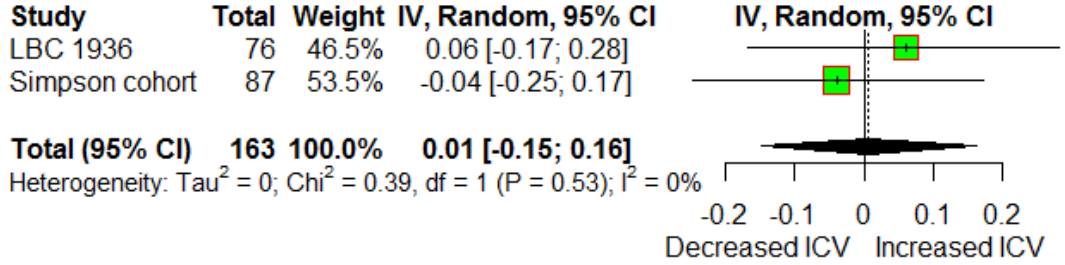
(i) Increasing ponderal index and global brain atrophy



(ii) Increasing ponderal index and whole brain volume

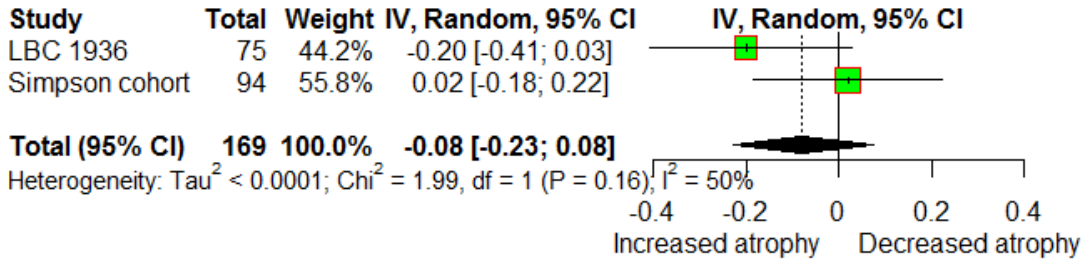


(iii) Increasing ponderal index and ICV

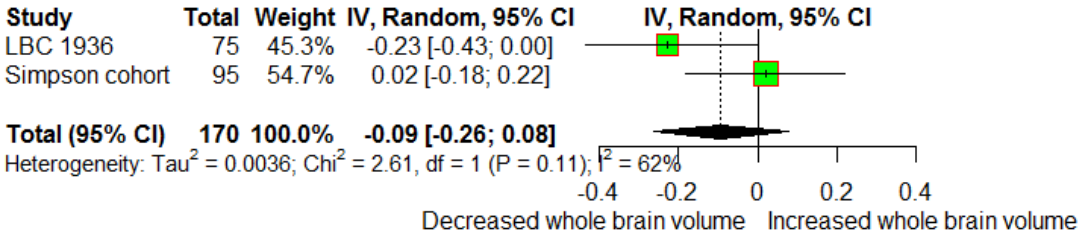


(E) Preterm

(i) Preterm and global brain atrophy



(ii) Preterm and whole brain volume



(iii) Preterm and ICV

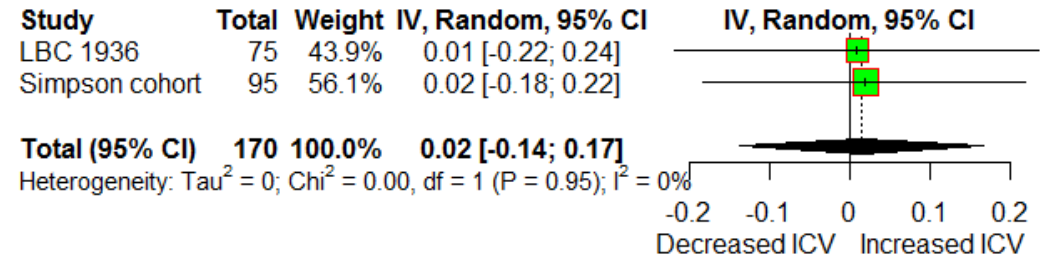


Figure 5.5 Meta-analysis of birth factors and brain volumes the LBC 1936 and Simpson cohort. Forest plots are presented for (A i-iii) increasing maternal age (B i-iii) increasing birth weight (C i-iii) increasing birth length (D i-iii) increasing ponderal index (E i-iii) preterm. All analyses are adjusted for age, sex, hypertension, smoking behaviour and adult SES.

Regional brain volumes

No birth factors were associated with the regional brain volumes in either cohort (Table 5.5).

Table 5.5: Birth factor associations with regional brain volumes in the Lothian birth cohort 1936 and the Simpsons cohort. All volumes are corrected for ICV.

All analyses are adjusted for and age, sex, hypertension, smoking behaviour and adult SES.

	LBC36		Simpsons	
	β	p	β	p
	Normal appearing white matter		**Frontal lobe volume**	
Maternal age	-0.08	0.36	0.1	0.35
Mother not married at birth	-	-	0.12	0.32
Ponderal index	0.11	0.37	0.01	0.96
Birth weight (g)	0.04	0.63	0.03	0.78
Birth length (cm)	-0.02	0.85	0.03	0.74
Preterm	-0.02	0.87	-0.01	0.95
Placental weight (g)	-	-	0.04	0.75
	Grey matter volume		**Temporal lobe volume**	
Maternal age	0.04	0.62	-0.15	0.13
Mother not married at birth	-	-	-0.02	0.87
Ponderal index	0.11	0.39	0.04	0.71
Birth weight (g)	-0.09	0.32	-0.13	0.26
Birth length (cm)	-0.12	0.30	-0.04	0.67
Preterm	-0.07	0.56	-0.03	0.73
Placental weight (g)	-	-	-0.13	0.26
	CSF volume		**AHC volume**	
Maternal age	0.04	0.65	-0.08	0.41
Mother not married at birth	-	-	0.03	0.77
Ponderal index	-0.05	0.68	0.04	0.70
Birth weight (g)	-0.02	0.86	-0.04	0.69
Birth length (cm)	-0.01	0.90	-0.11	0.30
Preterm	0.07	0.57	0.10	0.30
Placental weight (g)	-	-	0.04	0.76
	Right hippocampal volume		**Corpus collosum volume**	
Maternal age	0.02	0.81	-0.11	0.27
Mother not married at birth	-	-	0.05	0.67
Ponderal index	-0.06	0.59	-0.01	0.95
Birth weight (g)	0.11	0.19	0.00	0.97
Birth length (cm)	0.13	0.21	-0.03	0.78
Preterm	0.06	0.62	0.11	0.35
Placental weight (g)	-	-	-0.20	0.11

	Left hippocampal volume		Ventricular volume	
Maternal age	-0.12	0.17	0.06	0.57
Mother not married at birth	-	-	0.03	0.73
Ponderal index	0.05	0.66	-0.08	0.45
Birth weight (g)	0.08	0.27	-0.06	0.61
Birth length (cm)	0.01	0.88	0.03	0.79
Preterm	0.14	0.24	-0.11	0.42
Placental weight (g)	-	-	-0.07	0.56

CSF: cerebral spinal fluid; AHC: amygdala-hippocampal complex. All betas are standardised.

5.3.2.2 Childhood factors and brain volumes in the LBC 1936 and Simpson cohort

Total brain volume

Associations between childhood factors and total brain atrophy, total brain volume and ICV are presented in figure 5.6 A-H.

Across both cohorts increasing premorbid IQ was associated with decreased atrophy (β= 0.09, p=0.01) and higher whole brain volume in older age (β= 0.11, p=0.004, figure 5.6 Bi-ii).

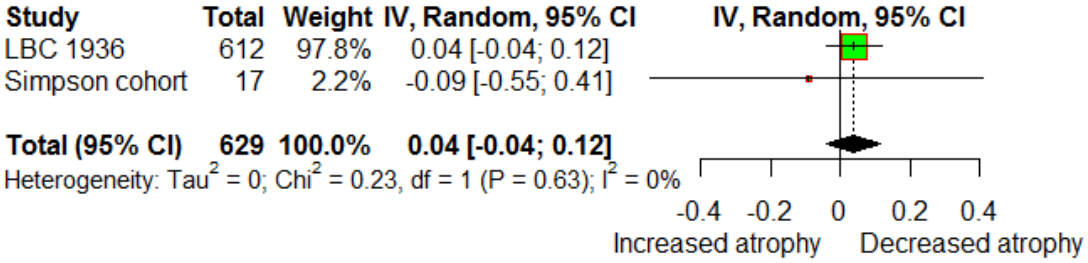
Across both cohorts increasing childhood IQ (β=0.08, p=0.04), increasing premorbid IQ (β=0.14, p<0.001) and increasing mean years of education (β=0.08, p=0.04) were associated with higher ICV (figure 5.6 A-C).

Across both cohorts there was a trend for having an outdoor toilet and increased whole brain atrophy but this did not reach statistical significance (β= -0.07, p=0.05, figure 5.6 F i). In the Simpson cohort only increasing overcrowding index was associate with increased total brain atrophy (β= -0.25, p=0.02) and decreased total brain volume (β= -0.27, p=0.01) (figure 5.6 H i-ii).

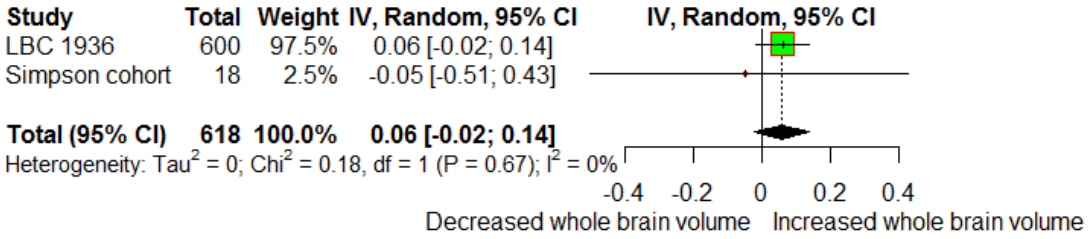
Figure 5.6 A-H Meta-analysis of childhood factors and ICV and total brain volume in the LBC 1936 and Simpson cohort. Forest plots are presented for (A i-ii) childhood IQ (B i-ii) premorbid IQ (C i-ii) mean years of education (D i-ii) low education (E i-ii) manual paternal SES (F i-ii) outdoor toilet (G i-ii) number of people sharing a toilet (H i-ii) overcrowding index. All analyses are adjusted for age, sex, hypertension, smoking behaviour and adult SES.

(A) Childhood IQ

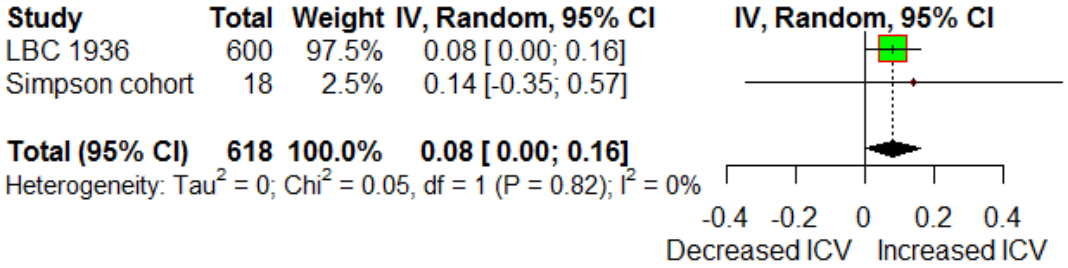
(i) Childhood IQ and whole brain atrophy



(ii) Childhood IQ and whole brain volume

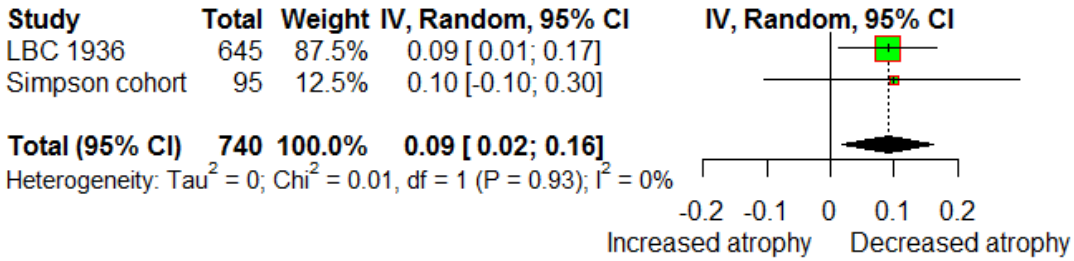


(iii) Childhood IQ and ICV

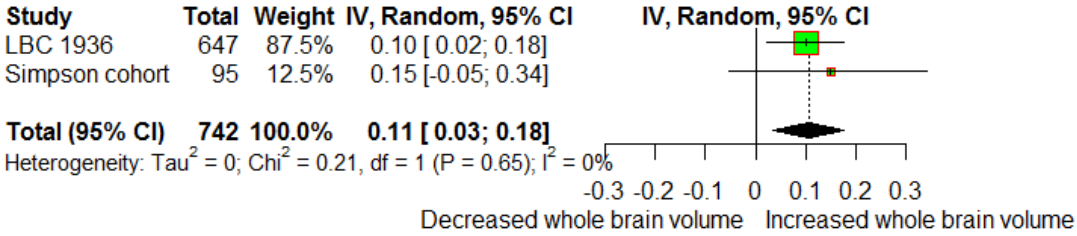


(B) Premorbid IQ

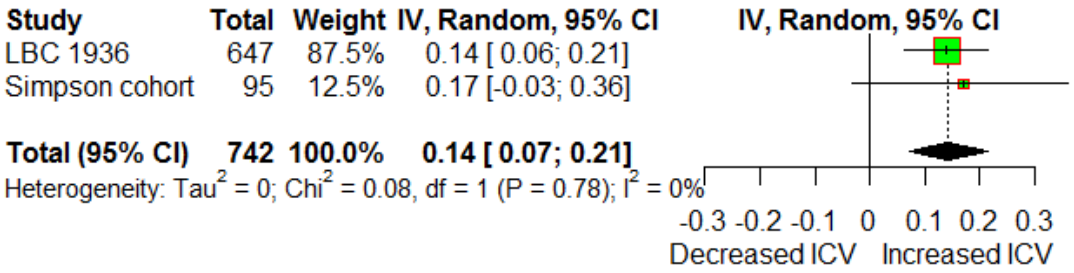
(i) Premorbid IQ and global brain atrophy



(i) Premorbid IQ and global brain volume

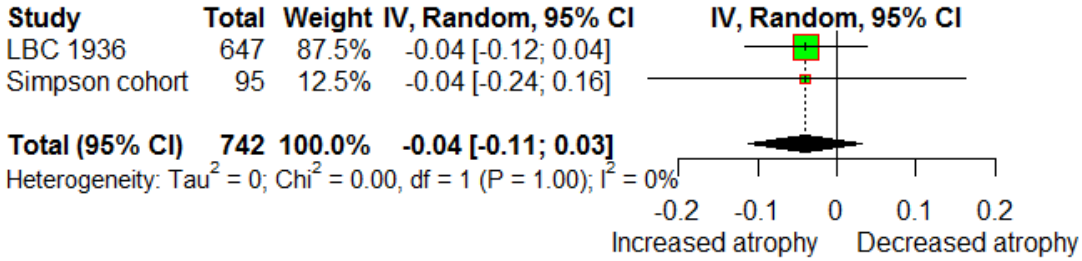


(ii) Premorbid IQ and ICV

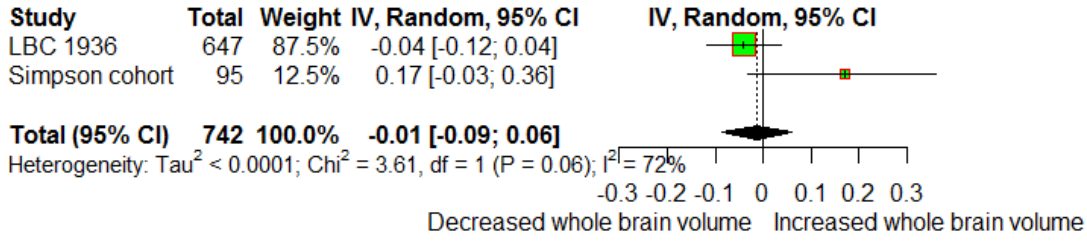


(C) Mean years of education

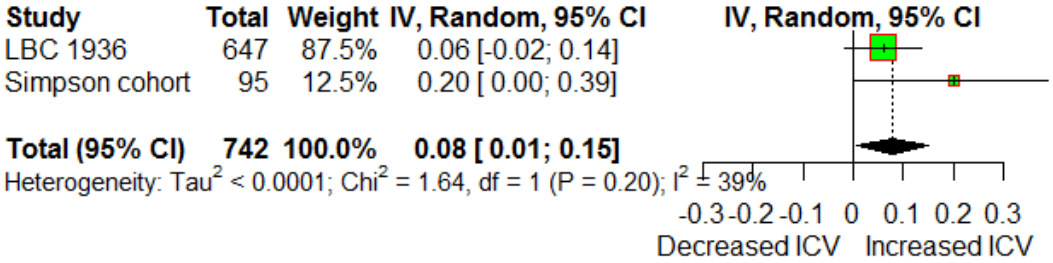
(i) Mean years of education global brain atrophy



(i) Mean years of education and whole brain volume

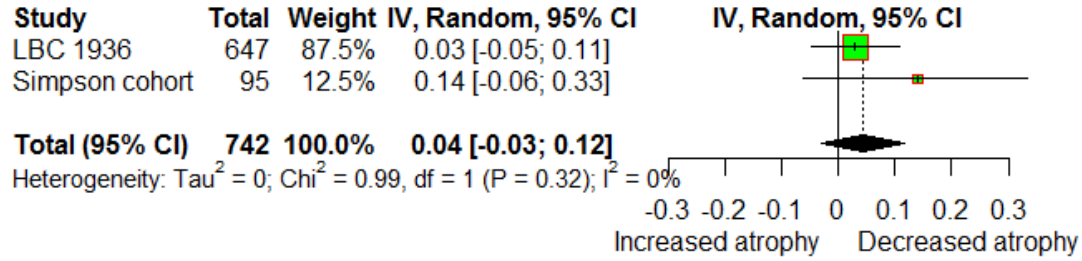


(ii) Mean years of education and ICV

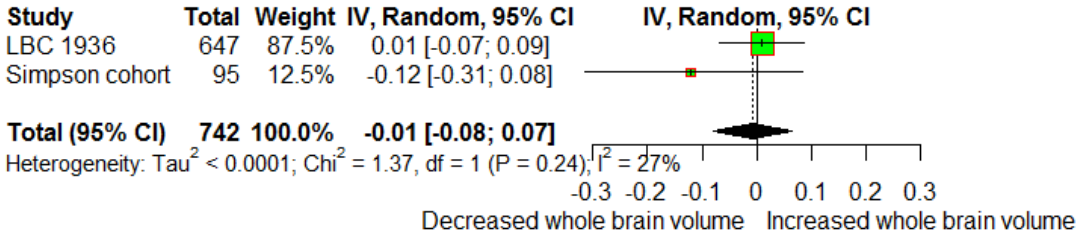


(D) Low education

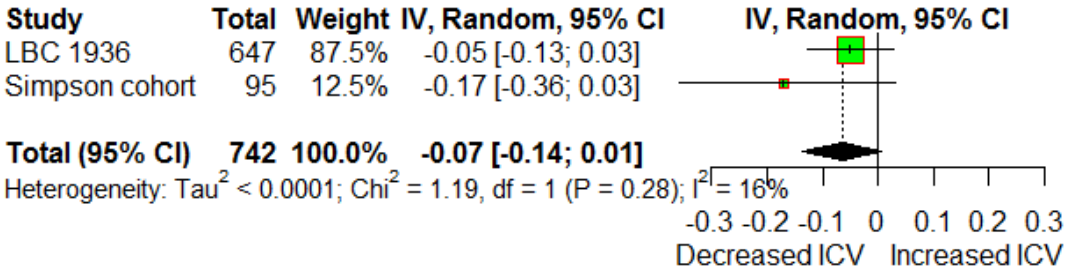
(i) Low education and whole brain atrophy



(i) Low education and whole brain volume

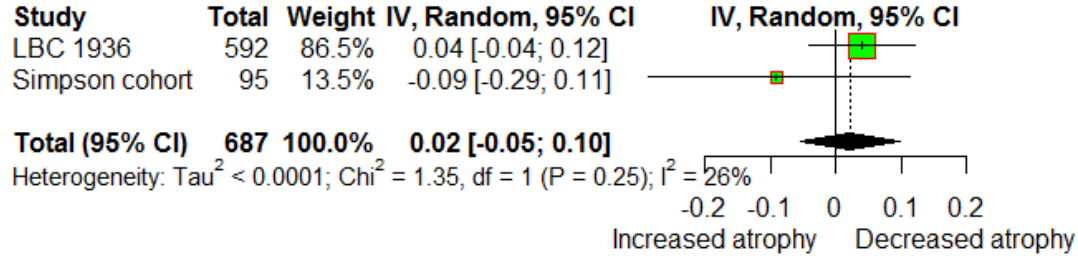


(ii) Low education and ICV

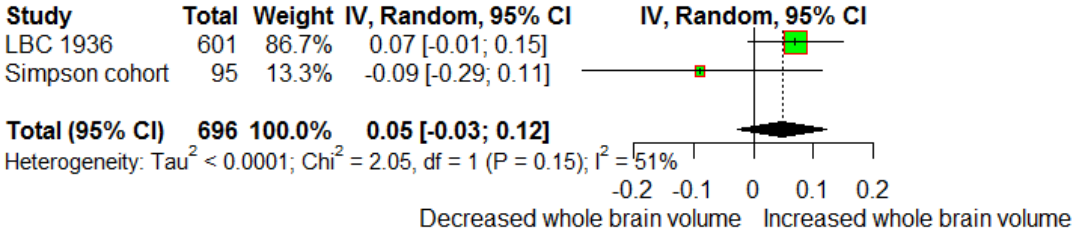


(E) Manual paternal occupation

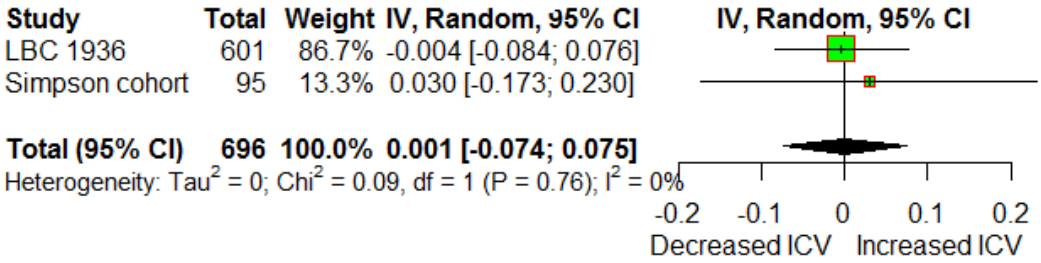
(i) Manual paternal SES and global brain atrophy



(i) Manual paternal SES and global brain volume

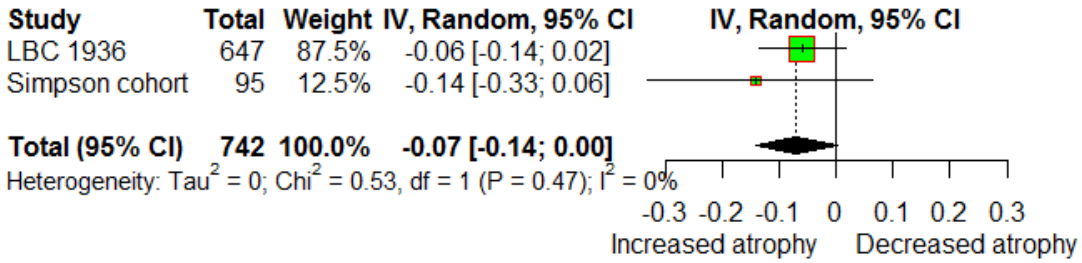


(ii) Manual paternal SES and ICV

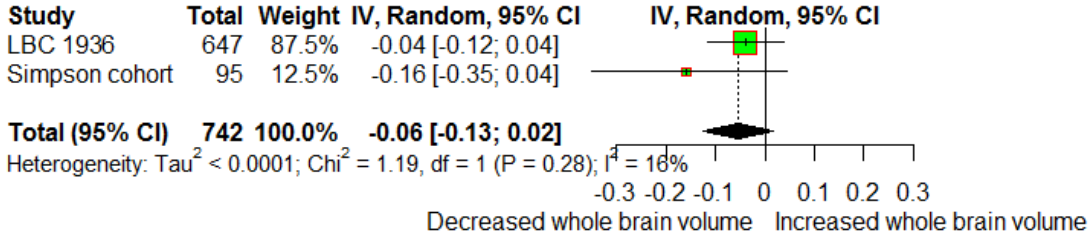


(F) Outdoor toilet

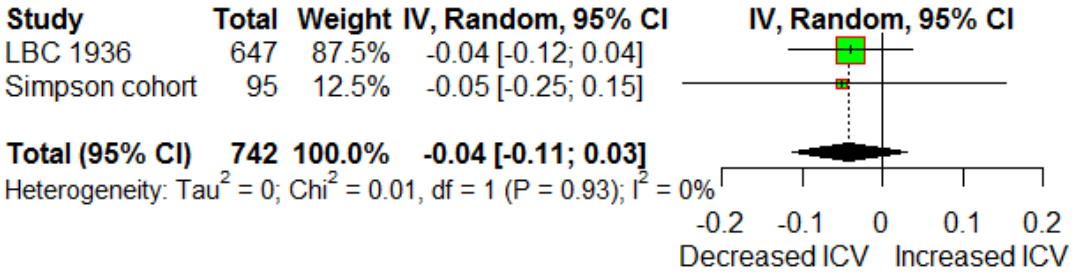
(i) Outdoor toilet and global brain atrophy



(i) Outdoor toilet and whole brain volume

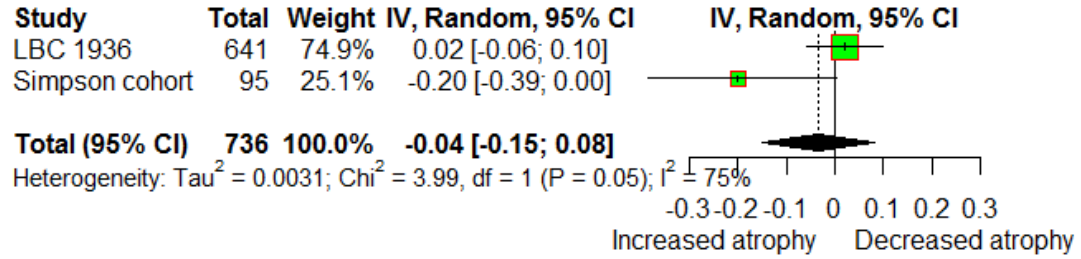


(ii) Outdoor toilet and ICV

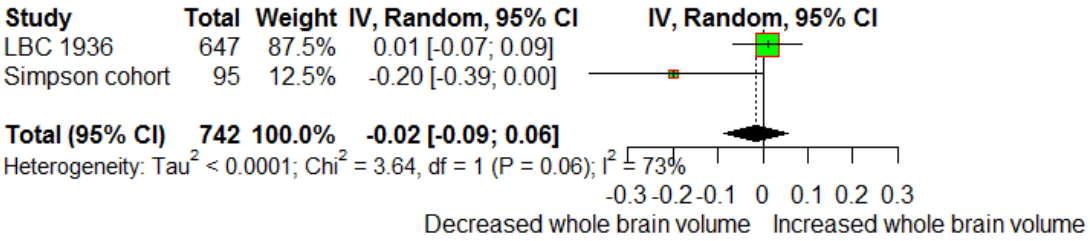


(G) Number of people sharing a toilet

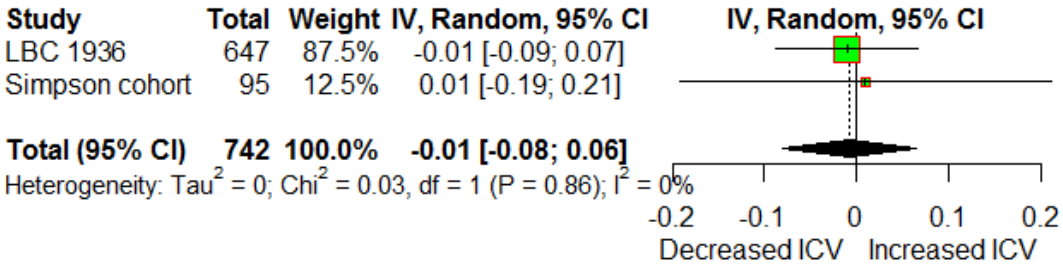
(i) Number of people sharing a toilet and global brain atrophy



(i) Number of people sharing a toilet and whole brain volume

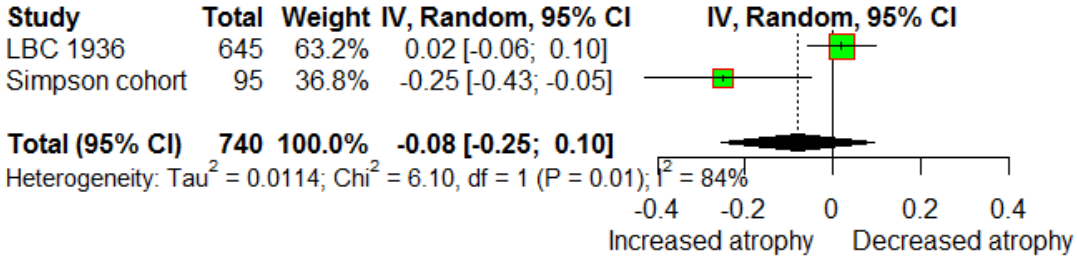


(ii) Number of people sharing a toilet and ICV

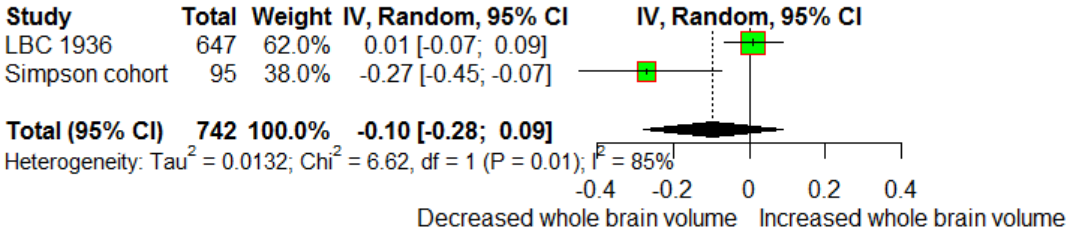


(H) Overcrowding index

(i) Overcrowding index global brain atrophy



(i) Overcrowding index and whole brain volume



(ii) Overcrowding index and ICV

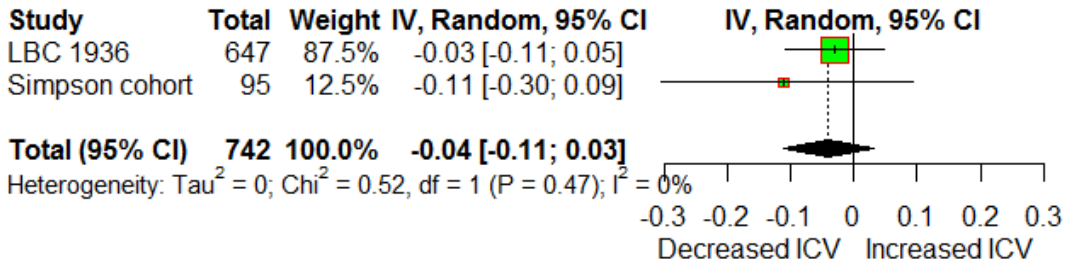


Figure 5.6 A-H Meta-analysis of childhood factors and ICV and total brain volume in the LBC 1936 and Simpson cohort. Forest plots are presented for (A i-iii) Childhood IQ (B i-iii) Premorbid IQ (C i-iii) Mean years of education (D i-iii) Low education (E i-iii) Manual paternal SES (F i-iii) Outdoor toilet (G i-ii) Number of people sharing a toilet (H i-iii) Overcrowding index. All analyses are adjusted for age, sex, hypertension, smoking behaviour and adult SES.

Regional brain volumes

Associations between childhood factors and regional brain volumes are presented in table 5.3.6.

In the LBC 1936 higher childhood IQ was associated with increased normal appearing white matter (β= 0.08, p=0.046) and increasing premorbid IQ was associated with increased right (β= 0.09, p=0.02) and left (β= 0.12, p=0.003) hippocampal volume.

Low education was associated with decreased right (β= -0.08, p= 0.03) and left (β= -0.09, p=0.02) hippocampal volume. Increasing mean years of education was associated with decreased grey matter volume (β= -0.01, p=0.01) in the LBC1936.

Manual Father's occupation was associated with higher grey matter volume (β= 0.01, p=0.01) in LBC1936. Having an outdoor toilet was associated with decreased normal appearing white matter (β= -0.09, p=0.02). Increasing number of people sharing a toilet was associated with increased frontal lobe volume (β=0.19, p=0.02) and decreased corpus collosum volume (β= -0.15, p=0.04). Increased overcrowding index as associated with decreased temporal lobe volume (β= -0.23, p=0.02) and decreased amygdala hippocampal complex volume (β= -0.30, p=0.001) in the Simpson cohort.

Table 5.6: Childhood factors associations with (a) whole brain volumes and (b) regional brain volumes in the Lothian birth cohort 1936 and the Simpsons cohort. All volumes are corrected for ICV.

(b)

	LBC36		Simpsons	
	β	p	β	p
	Normal appearing white matter		**Frontal lobe volume**	
Childhood IQ	**0.08**	**0.046**	-0.27	0.20
NART	0.11	0.11	-0.14	0.14
Education				
Mean years of education	-0.02	0.73	-0.03	0.77
Low vs high level of education	0.02	0.60	0.09	0.37
No qualifications vs > O level	0.01	0.87	-	-
Childhood SES				
Manual vs non manual	-0.04	0.26	0.1	0.31
Father's years of education	-0.01	0.87	-	
Outdoor toilet	**-0.09**	**0.02**	0.06	0.52
Number of people sharing a toilet	-0.03	0.51	**0.19**	**0.02**
Overcrowding index	-0.05	0.24	0.03	0.73
	Grey matter volume		**Temporal lobe volume**	
Childhood IQ	0.02	0.61	-0.15	0.52
NART	0.04	0.29	0.05	0.61
Education				
Mean years of education	**-0.1**	**0.01**	-0.09	0.39
Low vs high level of education	0.07	0.13	0.1	0.32
No qualifications vs > O level	0.04	0.35	-	-
Childhood SES				
Manual vs non manual	**0.1**	**0.01**	0.07	0.49
Father's years of education	-0.04	0.41	-	-
Outdoor toilet	0.001	0.97	-0.15	0.13
Number of people sharing a toilet	0.03	0.51	-0.08	0.41
Overcrowding index	0.04	0.27	**-0.23**	**0.02**
	CSF volume		**AHC volume**	
Childhood IQ	-0.04	0.34	0.02	0.95
NART	-0.06	0.12	0.14	0.22
Education				
Mean years of education	0.04	0.33	-0.11	0.19
Low vs high level of education	-0.02	0.66	0.09	0.22
No qualifications vs > O level	-0.05	0.24	-	-
Childhood SES				

Manual vs non manual	-0.05	0.17	0.15	0.22
Father's years of education	0.03	0.44	-	-
Outdoor toilet	0.05	0.14	-0.19	0.11
Number of people sharing a toilet	-0.002	0.96	-0.2	0.08
Overcrowding index	-0.01	0.77	**-0.3**	**0.001**
	Right hippocampal volume		**Corpus collosum volume**	
Childhood IQ	0.02	0.58	0.26	0.18
NART	**0.09**	**0.02**	-0.1	0.22
Education				
Mean years of education	0.002	0.97	-0.07	0.46
Low vs high level of education	-0.01	0.73	0.05	0.58
No qualifications vs > O level	**-0.08**	**0.03**	-	-
Childhood SES				
Manual vs non manual	0.01	0.72	-0.03	0.71
Father's years of education	0.01	0.85	-	-
Outdoor toilet	-0.02	0.65	-0.1	0.05
Number of people sharing a toilet	-0.003	0.93	**-0.15**	**0.04**
Overcrowding index	0.04	0.35	-0.12	0.13
	Left hippocampal volume		**Ventricular volume**	
Childhood IQ	0.03	0.41	0.06	0.76
NART	0.12	0.003	0.04	0.71
Education				
Mean years of education	0.01	0.8	0.13	0.21
Low vs high level of education	-0.02	0.66	-0.09	0.39
No qualifications vs > O level	**-0.09**	**0.02**	-	-
Childhood SES				
Manual vs non manual	0.03	0.42	0.06	0.52
Father's years of education	-0.02	0.55	-	-
Outdoor toilet	-0.05	0.21	-0.04	0.3
Number of people sharing a toilet	-0.004	0.91	-0.04	0.51
Overcrowding index	0.5	0.2	-0.04	0.55

CSF: cerebral spinal fluid; AHC: amygdala-hippocampal complex. All betas are standardised.

5.4 Discussion

5.4.1 Summary of findings

This study of early life influences on structural brain changes in four cohorts supports previous research suggesting that some early life factors may increase risk of cSVD, infarcts and brain volume loss in later life independent of vascular risk factors and adult SES. It further shows that some of these associations persist after adjustment for other early life factors. Meta-analysis found that increasing birth weight was associated with decreased risk of lacunes across all cohorts and increased ICV in the LBC 1936. Increasing placental weight, which was only available for the Simpson cohort, was associated with decreased total cSVD burden, WMH severity and volume, infarcts and ICV. Whilst not reaching conventional statistical significance many analyses were in the direction of worse early life factor associated with increased cSVD burden. Analyses in individual cohorts showed some additional statistically significant associations between birth factors and cSVD and brain volumes but these were not consistent across cohorts.

In STRADL, the LBC 1936 and Simpson cohort, increasing childhood and premorbid IQ and more years of education were associated with fewer infarcts, independent of education level and childhood SES. Childhood IQ was also associated with fewer WMHs, lacunes, lower total cSVD burden and higher ICV. Associations between childhood IQ and WMHs and lacunes were attenuated after additional adjustment for education and childhood SES. In the LBC 1936 and Simpson cohort increasing premorbid IQ was associated with lower global brain atrophy, higher whole brain volume and higher ICV. Across all four cohorts low education level was associated with more micro-bleeds and higher ICV in the LBC 1936 and Simpson cohort. Manual parental occupation was not associated with any markers of cSVD or brain volumes in the meta-analysis. In the LBC 1936 increasing overcrowding index was associated with increased global brain atrophy and decreased whole brain volume. Some additional measures of childhood SES, only available in the LBC 1936 and Simpson cohort (outdoor toilet, number of people sharing a toilet, overcrowding index), were associated with cSVD but none of these reached statistical significance in the meta-analysis.

These findings are consistent with the suggestion that factors other than traditional vascular risk factors may contribute to cSVD pathology and structural brain changes

in later life. However the effect sizes are small and there are limitations, as well as strengths which are discussed in section 5.4.4.

5.4.2 Birth parameters and structural brain changes.

The relationship between birth factors and brain structure is biologically feasible: lack of nutrients or oxygen at particular stages of gestation can impair foetal growth resulting in small size at birth, indicated by low birth weight, birth length and small head circumference, or disproportionate growth such as large head to body ratio or low weight to length ratio (ponderal index). A small abdomen in relation to head circumference was originally thought to be due to 'brain sparing' whereby in times of scarcity, nutrients and oxygen are diverted away from the trunk to the brain at the expense of other organs such as the liver or pancreas (Barker, 2004). This was thought to protect the brain, however more recently it has been shown that restricted growth is associated with poorer cognitive outcomes in childhood and later life, suggesting that an adverse prenatal environment may have lasting effects on brain development (Grove et al., 2017). Recent studies have replicated the original studies conducted by Barker and colleagues such that relations between birth weight, birth length and ponderal index, and overt vascular or metabolic diseases in later life are well established (Risnes et al., 2011, Wang et al., 2014c). For example small birth weight is associated with a range of diseases or abnormalities of homeostasis including coronary heart disease (Wang et al., 2014c), all-cause mortality and cardiovascular mortality (Risnes et al., 2011) and type 2 diabetes (Li et al., 2015).

The placenta is the sole source of transfer of oxygen and nutrients from mother to baby and therefore plays a key role in foetal growth (Barker, 1995). Placental efficiency is dependent on placental size, form and structure which can be influenced by maternal nutrition (Burton et al., 2016). Low placental weight (Heshmati and Koupil, 2014, Fan et al., 2010), small placental surface area (Barker et al., 2010b, Eriksson et al., 2011) and large placenta in relation to birth weight (Hayward et al., 2016, Barker et al., 2012) have been associated with higher risk of adult cardiovascular disease. Previous research has suggested that a mother's ability to sustain normal placental growth is influenced by body shape, height and socioeconomic status which are thought to reflect her nutritional history. Barker and colleagues found that low placental weight and area were associated with increased hypertension in the offspring of mothers who were short or of low SES. The opposite was found in the children of those who were tall and middle class (Barker et al.,

2010a), suggesting that the association between placental weight and health in the offspring may be moderated by the SES of the mother. The present analysis found an association between increasing placental weight and lower cSVD burden in all participants not just those from families of low SES. In the Simpson cohort a large proportion (88%) were from families of low SES which may explain these differences in findings. It is possible that associations between placental weight and cSVD may be stronger in participants from lower socioeconomic backgrounds but this was not examined in the present analysis.

There are far fewer studies which have examined these birth parameters and cerebrovascular disease. Large epidemiological studies have shown an association between birth weight or placental weight and stroke incidence and mortality (Barker, 1997, Barker and Lackland, 2003), but the present analysis is one of the first to examine birth parameters and cerebrovascular disease and cSVD on MRI. Previous research in the Dutch Famine Birth Cohort has found that foetal malnutrition can lead to accelerated cognitive aging (de Rooij et al., 2010) and advanced structural brain aging, measured using the BrainAGE method (a composite measure based mainly on tissue loss) (Franke et al., 2017). However another previous study in this cohort found no association between famine exposure and WMH volume, white matter integrity and total brain volume after correction for ICV (de Rooij et al., 2016) which is consistent with the current findings. The present study has further shown no association between famine exposure and other cSVD markers in a subgroup of the Dutch Famine Birth Cohort with imaging data.

A previous study (Shenkin et al., 2009) in the Simpson cohort examined birth weight, birth length and placental weight and WMH burden and white matter diffusion tensor magnetic resonance imaging (DT-MRI) parameters indicative of white matter integrity. It found a correlation between higher placental weight and decreased WMH burden (measured using the Fazekas scale) and increased white matter integrity. Birth weight was associated with white matter integrity in the frontal lobes only. The present study supports previous findings in the Simpson cohort and adds to the evidence that placental weight is associated with WMH burden. It further demonstrates that placental weight may influence total cSVD burden and risk of infarcts. Placental weight was only available for the Simpson cohort which has a small sample size and so further research in larger samples are needed to confirm these findings. There was

no association between placental volume, area or area to birth weight ratio and cSVD in the Dutch Famine Birth Cohort.

Data from other cohorts have been mixed. The (AGES)-Reykjavik study (RS) (Muller et al., 2014) found that low ponderal index was associated with smaller total brain volumes and white matter volumes at age 75 but the association with WMH volumes was no longer statistically significant after adjustment for adult vascular risk factors. The present study is consistent with the (AGES)-Reykjavik study in that it found no association between ponderal index and WMH assessed either visually using the Fazekas scale or as a volume. However the present study also found no association between ponderal index and total brain volume. The number of participants in this study who had available birth size and brain volume data (188) was considerably smaller than the 1,254 participants in the (AGES)-RS cohort which may explain some of the differences in findings. However the effect size found here (β= -0.03) was lower compared to the effect size in the (AGES)-Reykjavik study (β= -1.00).

5.4.3 Childhood factors and structural brain changes

From a life course perspective, a disadvantaged foetal environment may interact with factors during childhood to increase risk of later disease. Development of neural pathways in the brain extends well into childhood and may therefore mean the brain remains vulnerable to insults for a longer period of time (Walker et al., 2011). Higher childhood intelligence is inversely associated with many health outcomes across the life course, including mortality, vascular dementia and stroke (Deary et al., 2003) (Batty et al., 2005, Shipley et al., 2008). The meta-analysis presented in chapter 2 identified 5 previous studies, one of which was on the LBC 1936, which had examined childhood IQ and WMH burden and found that overall childhood IQ was negatively correlated with WMH burden. Additional research in the LBC 1936 and the Simpson cohort, not included in the meta-analysis, also found that higher premorbid or childhood IQ was associated with higher white matter integrity in the centrum semiovale (Deary et al., 2006, Shenkin et al., 2003) and lower total cSVD score (Field et al., 2016). Few of these studies adjusted for health related behaviours or vascular risk factors, adult SES or other early life factors which is an important factor to consider when interpreting these results, especially given the complex interrelationships between risk factors for cerebrovascular disease. This analysis built on the meta-analysis in chapter 2 and previous research in the LBC 1936 and Simpson cohort, adjusting all models for age, gender, hypertension, smoking

behaviour and adult SES. The point estimate for the association between childhood IQ and WMH volume (B= -0.06 95% CI -0.14 – 0.01) and microbleeds (OR 0.98 95% CI 0.94- 1.01) were in the expected direction but did not reach statistical significance in this analysis. This study did find that higher childhood and premorbid IQ were associated with fewer infarcts and childhood IQ was associated with fewer WMHs, lacunes and total cSVD burden. This is the first study to report these findings and suggests that higher childhood and premorbid IQ may be protective of multiple markers of cSVD.

General intelligence and brain size show consistent modest, correlation in both children and adults (Pietschnig et al., 2015). The present study found higher childhood and premorbid IQ were associated with larger ICV (an estimate of maximal brain size). Furthermore premorbid IQ was associated with lower whole brain atrophy and larger total brain volume (corrected for ICV). It has been proposed that possessing a larger brain provides some resistance against neurodegeneration in later life which can reduce cognitive decline (Stern, 2012). Some researchers have suggested that this association is due to the persistence of the relationship between brain volume and cognition from earlier in life. In the LBC 1936, previous research has shown that age 11 IQ predicts cortical thickness in later life and accounts for over two-thirds of the cross sectional association between cognitive ability and cortical thickness in later life (Karama et al., 2014). This study also found that increasing years if education was associated with increased ICV, a measure of maximum brain size. Longer education duration is associated with greater cortical thickness (Kim et al., 2015) and cerebral (Foubert-Samier et al., 2012) or grey matter (Arenaza-Urquijo et al., 2013) volume. However this study found that mean years of education was associated with decreased grey matter volume. Having no qualifications was associated with decreased hippocampal volume. The present study cannot determine the direction of effect i.e. whether a smaller brain leads to less education or whether less education leads to a smaller brain.

The meta-analysis in chapter 2 found that low education (defined either by attainment or years) was associated with a 35% increased risk of stroke and a 17% increased risk of cSVD. The present study used several measures of education and the analysis produced mixed results. Contrary to the meta-analysis, the present study found no association between low education level and WMH burden. This may partly be explained by the sample size which, although at 1166 is relatively large, is much

smaller than the 23,000 and >5,000,000 participants included in the meta-analyses. It may also be due to the definitions of high and low education. High and low education level were calculated for each cohort based on the information collected in each study to allow direct comparison of the cohorts. The definition of 'low education' was relatively crude due to the different data collected in each study and the differences among the Dutch and Scottish education system in the 1930s. As there was heterogeneity between the studies a random effects model was used in the meta-analysis. No significant heterogeneity (measured using I^2) was found between studies which suggests that these differences will not have impacted significantly on the analysis. However, there are likely additional differences between the cohorts which will not be taken into account in the random effects model and will not be reflected in the I^2. Although this study found no associations between education and WMH, it is one of the first studies to report associations between education and micro-bleeds (low education level across the three cohorts and having no qualifications in the LBC 1936 increased risk of micro-bleeds) and infarcts (mean years of education was associated with decreased risk of infarcts in the LBC 1936 and Simpson cohort).

In the present study manual parental occupation was not associated with increased cSVD. In some of the analysis, manual parental occupation was actually associated with lower cSVD burden. This is not consistent with the meta-analysis in chapter 2 which found a significant association between childhood SES (manual paternal occupation) and increased WMH (in one study) and a 28% increased risk of stroke (in 10 studies). These contradictory findings may be due "cohort inversion". This occurs when selective mortality removes persons with the most health problems first which can invert previous associations and make groups that were initially disadvantaged appear advantaged (Ferraro and Shippee, 2009). Alternatively, using parental occupation, collected at one time point may not fully capture childhood experiences. Unforeseen circumstances, such as recession or illness may result in short term unemployment which may have a limited impact on the child, or long term unemployment which may lead to reduced resources and increased stress experienced by the child. It is also important to note that parental occupation in these cohorts may have been affected by the First or Second World War and so may not be truly representative of childhood circumstances or SES

A strength of this study is the availability of additional measures of childhood SES in two of the cohorts. Having an outdoor toilet and more people sharing a toilet was

associated with increased risk of infarcts in the Simpson cohort but not the LBC 1936. This may be due to historical differences between the cohorts or may be due to chance or bias, the effect sizes are small and some of the confidence intervals are large and must therefore be interpreted with caution. Previous research in the LBC 1936 has shown associations between cSVD and deprivation index (Field et al., 2016) (moderate/severe cSVD: OR 1.08 95% CI 1.00-1.17). It may be that deprivation index, which encompasses several of these socioeconomic markers into one variable, is more strongly associated with cSVD in later life than parental occupation or individual markers of household circumstances. The relationship between childhood SES and cSVD is complicated and there is a need to include complex measures of social deprivation across the life course.

The lack of statistically significant associations between some of the early life factors and cSVD and brain volumes in these cohorts may be due to lack of power as the sample sizes are relatively small. The participants in these cohorts were also a select group of relatively young (mean age 70), community dwelling volunteers. Volunteers are generally healthier and of higher social class than non-volunteers (Deary et al., 2012). Even in the oldest cohort, less than 30% of participants had moderate or severe cSVD. The Dutch Famine Birth Cohort has demonstrated excess mortality up to the age of 63 years in women exposed to famine in early gestation (van Abeelen et al., 2012). This may have resulted in selective participation of people who were in sufficient health to participate in the present study at age 68. It may be that associations between early life factors and cSVD are stronger in older individuals with more severe vascular disease who had already died before the start of the present study.

Educational attainment is strongly related to both cognitive ability and SES and education is often used as an indicator of SES. Several researchers have suggested that education may be a surrogate for cognitive ability but their relationship has been widely debated (Deary and Johnson, 2010). These relationships may be bidirectional, for example unfavourable socioeconomic circumstances can restrict opportunities for or access to higher education. IQ may influence educational choices with more intelligent people accessing higher or further education. IQ may also lead to more educational success, better employment opportunities and access to other socioeconomic benefits associated with achieving better health. To assess the independence of associations between cognitive ability, education and childhood SES

multiple regression analyses were performed, adjusting for early life factors and vascular risk factors. All associations were attenuated but the association between both childhood IQ and premorbid IQ and infarcts remained statistically significant. This suggests that the association between premorbid IQ or childhood IQ and infarcts may be independent of education level.

Several mechanisms may account for the associations between early life factors and health in later life. Evidence suggests that foetal origins of adult disease may be caused in part by excess exposure to corticosteroids during gestation, either through excess maternal corticosteroids, dysfunction of the placental barrier or through exogenous administration (Reynolds) . Exposure to glucocorticoids in utero may slow foetal growth resulting low birth weight babies (Bloom et al., 2001) and babies who are small for gestational age (Goedhart et al.). It may also alter the set point of the foetal hypothalamic-pituitary adrenal (HPA) axis. Hyperactivity of the HPA axis negatively affects foetal development and can result in increased risk for later disease. Elevated cortisol levels and increased adrenal responsiveness to adrenocorticotropic hormone (ACTH) in adulthood is associated with low birth weight and increased blood pressure, insulin resistance, glucose intolerance and plasma triglyceride levels (Phillips et al., 1998, Reynolds et al., 2001, Reynolds et al., 2005).

Children from higher socioeconomic backgrounds are likely to be exposed to better diets and medical care and more educational opportunities and hence may have more job opportunities or less hazardous working conditions. In adulthood they may be more likely to engage in better lifestyle behaviours and self-management of vascular risk factors. Notably the lack of associations between childhood SES tends to suggest that the mechanism is not simply that that lower early life factors lead to failure to adopt public health messages or unhealthy lifestyles or adult SES. Alternatively positive early life factors may be associated with, or lead to, an increase in the resilience and integrity of the brain resulting in less cSVD.

5.4.4 Strengths and limitations

The strengths of the current study included the availability of prospectively collected early life data on older-age participants which is rare. Birth data was recorded at the time of birth, and therefore did not rely on retrospective estimations of birth weight which in other studies has raised concerns of recall bias. Detailed birth records allowed correction for gestational age and placental measures which are not always

available. Birth weight was used to calculate ponderal index as a measure of infant growth. This may be a better indicator of problems than birth-weight percentiles as it provides information on the neonate's body proportionality and can detect situations in which weight growth exceeds or fails to keep up with growth in the infant's length. The present analysis adjusted for vascular risk factors and other early life factors and had a relatively large sample size for some analyses.

There were limitations. There was relatively low cSVD burden in the cohorts and birth data were only available for a subset of participants in the LBC1936. The Dutch Famine Birth Cohort and the Simpson cohort also only included people who were born in hospitals and not those born at home. The samples came from Scotland and the Netherlands which may introduce confounding effects due to local variations in socioeconomic strata. Furthermore the education system in the Netherlands is different to Scotland and the division into 'low' and 'high' education level was relatively crude. Whilst the models were adjusted for key vascular risk factors the sample size did not allow adjustment of other risk factors. It was also not possible to separate the confounding effects of maternal stress, smoking during pregnancy or other prenatal environmental or genetic influences which may affect foetal brain development. Finally this chapter examined a large number of early life factors and did not adjust for multiple testing which may mean that some associations are due to chance.

5.4.5 Conclusions

These findings suggest an important albeit small effect of early life factors, particularly IQ, on brain vascular disease in later life independent of common vascular risk factors, adult SES and other early life factors. Early life factors such as better childhood cognitive ability may protect against later risk of cerebrovascular disease although these associations may be confounded by other genetic or environmental factors. Childhood cognitive ability may influence health behaviours and access to socioeconomic resources beneficial to health. Additionally they may increase brain integrity and resilience leading to reduced susceptibility to cerebrovascular disease. Brain vascular disease increases risk of cognitive impairment and dementia and stroke and worsens chances of recovery after stroke. The current findings may provide the mechanistic link between the known associations between early life factors and risk of stroke and dementia. Health disparities are well known and these findings suggest that such disparities can persist across decades of life. This

highlights the importance of identifying modifiable factors that may be targets for future social policy interventions.

6. Early life factors and symptoms of anxiety and depression

6.1 Introduction

Depression and anxiety are highly prevalent diseases and often appear as comorbid disorders (Kvaal et al., 2008). Depression has been recognised as a major mental health problem in older adults. The World Health Organisation (WHO) predict that by 2030 it will be the leading cause of burden of disease as measured by disability adjusted lived years (World Health Organization, 2009). Common risk factors in later life include disability and poor health, bereavement and prior depression (Aziz and Steffens, 2013). However exposures during early years of life including during pregnancy may have an important role in its aetiology. There is some evidence that prenatal malnutrition is associated with increased self-reported depression below the age of 60 (Stein et al., 2009, Brown et al., 2000) but this is not supported by all studies (de Rooij et al., 2011). Furthermore, meta-analysis has found that low birth weight significantly increased the odds of developing depression in adulthood (Loret De Mola et al., 2014). Studies which have examined these early life factors and mental health in older adults have produced mixed results. Thompson and colleagues reported that foetal undernutrition predisposed men, but not women to depression at age 68 (Thompson et al., 2001). More recently, lower birth weight was related to lifetime depression in a sample of Swedish women who were followed up at age 92 (Gudmundsson et al., 2011). On the other hand Gale and colleagues and Skogen and colleagues both found no association between birth weight and depression at age 64-74 (Gale et al., 2011, Skogen et al., 2013).

Depression and anxiety have been consistently shown to occur more frequently in those from more disadvantaged backgrounds. A handful of studies find that low cognitive ability in early life, low education level and low childhood socioeconomic status (SES) may increase liability for mental health disorders in adulthood (Gale et al., 2008). For example a study of 22,777 people aged 50-104 across 10 European countries reported that odds of late-life depression were twice as high in adults with less than a high school education compared to those with higher levels (Ladin, 2008). In older adults, cognitive impairment is often reported in those with depression (Rock et al., 2014). However whether poor cognition is a consequence or a risk factor for depressive symptoms remains unclear. There is evidence in the literature of a link between intelligence test scores in childhood or early adulthood and risk of later

depressive symptoms (Gale et al., 2011, Wraw et al., 2016, Gale et al., 2010). However much of the previous work has examined mental health outcomes in young adulthood or midlife. Few studies have examined factors from early childhood and mental health in older adulthood.

Many previous studies are based on records of hospital admissions for mental illness rather than measures of symptoms of anxiety or depression. However it has been reported that the prevalence of depressive symptoms that do not meet the full diagnosis criteria for major depression could be as high as 16% in the general older adult population (Meeks et al., 2011). These symptoms are a strong predictor for subsequent major depressive disorder (MDD). Furthermore they are associated with similar risk factors and functional and medical comorbidities to those found in MDD (Rodríguez et al., 2012). Neuroimaging studies have also reported reductions in grey matter volumes and white matter integrity in those with late-life subthreshold depression similar to that seen in patients with MDD (Tudorascu et al., 2014, Hayakawa et al., 2013, Dotson et al., 2009). Symptoms of anxiety disorder that do not meet the criteria for general anxiety disorder (GAD) are twice as common as clinically diagnosed GAD and are also associated with considerable impairment (Haller et al., 2014). Therefore this chapter will examine whether early life factors are associated with symptoms of anxiety and depression in older adults. Increasing understanding of relationships can inform psychiatric disorder prevention programs and reduce distress and disability to at risk groups.

The first aim of this chapter was to examine the relationships between (a) birth parameters (mainly birth weight, birth length and ponderal index) and (b) childhood factors (childhood and premorbid IQ, education and measures of childhood SES) and depressive symptoms on 1) the depression subscale of the HADS (HADS-D) in the Dutch Famine Birth Cohort, the LBC 1936 and the Simpson cohort and 2) the QIDS-16 in the STRADL cohort

The second aim was to examine the relationships between (a) birth parameters (mainly birth weight, birth length and ponderal index) and (b) childhood factors (childhood and premorbid IQ, education and measures of childhood SES) symptoms of anxiety on the anxiety subscale of the HADS (HADS-A) in STRADL, the Dutch Famine Birth Cohort, the LBC 1936 and the Simpson cohort.

The third aim was to examine the independence of any associations between early life factors and symptoms of depression and anxiety by conducting a series of multiple regression analyses.

6.2 Methods

The methods for recruitment, measurement of birth and childhood factors and neuropsychiatric data are presented in detail in Chapter 3.

6.2.1 Participants

STRADL

This chapter uses data from 280 STRADL participants with demographic and neuropsychiatric data. Depressive symptoms were measured using the QIDS-16 and symptoms of anxiety were measured using the HADS-A.

The Dutch Famine Birth cohort

151 members of the Dutch Famine Birth Cohort are included in this chapter. This includes 41 participants who were exposed to famine in early gestation, 42 exposed to famine during preconception and 35 participants born before the famine who were therefore unexposed to famine in utero. Most demographic and neuropsychiatric data is available for all participants. Depressive symptoms were measured using the HADS-D and symptoms of anxiety were measured using the HADS-A.

The Lothian Birth cohort 1936

Data from wave 2 of the Lothian Birth Cohort study is included in this chapter: 866 LBC 1936 participants provided demographic information and completed neuropsychiatric assessments. Depressive symptoms were measured using the HADS-D and symptoms of anxiety were measured using the HADS-A.

The Simpson Cohort

One hundred and thirty people provided some demographic and neuropsychiatric data. Depressive symptoms were measured using the HADS-D and symptoms of anxiety were measured using the HADS-A.

6.2.3 Statistical analysis

Descriptive characteristics were calculated using means and standard deviations (SD), medians and interquartile ranges or counts and percentages as appropriate. Differences in demographic characteristics, symptoms of anxiety and depression and early life factors between the four cohorts were analysed using Chi-squared tests, Krustal Wallis tests and ANOVAS with Bonferroni corrected p-values.

Associations between early life factors and symptoms of anxiety and depression were analysed using multiple linear regression. Bootstrapping was used for analyses with non-normally distributed residuals. Due to the sample size of the individual cohorts and the number of and similarities between the early life factors it was not possible to adjust for other early life factors in addition to vascular risk factors in all models. Therefore each early life factor was analysed separately and adjusted for age, sex, hypertension, smoking behaviour and adult SES and cognition. Specific early life factors were then selected and added to the same model in addition to vascular risk factors, adult SES and cognition. As previous research has found stronger effects of famine exposure on psychiatric symptoms in men, this study tested for possible interaction effects by adding an interaction term sex x famine exposure to the models.

Scores on the HADS-D (seven items, range 0-21) or QIDS-16 (16 items, range 0-27) and HADS-A (seven items, range 0-21) were analysed separately. Each cohort was analysed separately and then meta-analysed to maximise sample size. Regression analyses were performed using SPSS version 22 (IBM Corp, 2013) and meta-analyses were performed using the package metacor for R v3.3.2 (R Core Team, 2016).

6.3 Results

Demographic and key characteristics of all participants are displayed in Table 6.1.

STRADL participants (n=280) had a mean age of 62.1 (SD 4.1) and were 45% male. The Dutch famine cohort (n=151) had a mean age of 67.6 (SD 0.9) and was 44% male. The LBC 1936 (n=866) had a mean age of 72.7 (SD 0.7) and was 52% male. The Simpson cohort (n=130) had a mean age of 78.4 (SD 1.5) and was 31% male.

Health behaviours and vascular risk factors varied between cohorts. The percentage of participants with high blood pressure (χ^2 (3) = 129.2, p<0.001) diabetes (χ^2 (3)= 44.3, p<0.001), current or ex smokes (χ^2 (3)= 11.64, p=0.01 and manual adult SES (χ^2 (3)= 118.1, p<0.001) differed between cohorts. High blood pressure was most common in the Dutch Famine Birth Cohort (54.7%) and lowest in STRADL (12.3%). Diabetes was also most common in the Dutch Famine Birth Cohort (54.7%) and least common in STRADL (1.1%). There were the most current or ex-smokers in the Dutch Famine Birth cohort (62.4%) and the fewest in STRADL (47.70%). The Simpson cohort had the highest percentage of participants with manual adult SES (62.3%) and the LBC 1936 had the fewest (20.7%).

Symptoms of depression and anxiety were different between the cohorts and appeared to increase with increasing age of the cohorts (χ^2 (2) = 46.78, p<0.001; χ^2 (3) = 23.87, p<0.001). The median HADS-D scores were 2 (Dutch Famine Birth Cohort and LBC 1936) and 4 (Simpson cohort). Dunn's post hoc pairwise tests with Bonferroni adjusted p values showed that the Simpson cohort scores significantly higher than the Dutch Famine Birth Cohort (p<0.001) and the LBC 1936 (p<0.001). HADS-D scores were not available for STRADL participants but median QIDS-16 score was 3 (maximum score of 27). The median HADS-A scores were 3 (STRADL), 4 (the Dutch Famine Birth Cohort and the LBC 1936) and 5 (Simpson cohort). Dunn's post hoc pairwise tests were carried out to examine differences between each cohort with Bonferroni adjusted p values. The Simpson cohort scored significantly higher than the LBC 1936 (p=0.01) and STRADL (p<0.001). And STRADL participants scored significantly lower than LBC 1936 participants (p=0.01).

Birth weight was similar across the Dutch Famine Birth Cohort, the LBC 1936 and the Simpson cohort (F(2)= 2.70, p=0.07). Birth length (F(2)= 4.27, p=0.02) and ponderal index (F(2)= 4.72, p=0.01) were different between cohorts. Post hoc tests with

Bonferoni corrections showed that the Dutch Famine Birth Cohort had significantly higher birth length compared to the LBC 1936 and the LBC 1936 had significantly higher ponderal index compared to the Simpson cohort. These data were not available for STRADL participants.

Childhood IQ was similar across STRADL, the LBC 1936 and the Simpson cohort ($F(2)= 1.06$, $p=0.35$).The percentage of participants with low education differed between the cohorts (χ^2 $(3)= 23.0$, $p<0.001$). The percentage of participants with low education was 64.4 (STRADL), 60.3% (Dutch Famine Birth Cohort), 72.5% (LBC 1936), 82.3% (Simpson cohort). There was no difference in childhood SES between cohorts (χ^2 $(3)= 4.0$, $p=0.30$).

Table 6.1: (A) Demographic and health characteristics and (B) early life characteristics of STRADL, the Dutch famine birth cohort, the Lothian Birth Cohort and the Simpson cohort. Information is displayed separately for each cohort.

A

	STRADL		Dutch Famine		LBC1936		Simpsons	
	Total N	N (%)	Total N	N (%)	Total N	N (%)	Total N	N (%)
Sex, male	280	126 (45.0)	151	67 (44.4)	866	448 (51.7)	130	40 (30.8)
Age (y), mean (SD)	280	62.1 (4.1)	151	67.6 (0.9)	866	72.7 (0.7)	130	78.4 (1.5)
Health covariates: history								
Hypertension	276	34 (12.3)	150	82 (54.7)	866	425 (49.1)	130	63 (48.5)
Diabetes	276	3 (1.1)	151	29 (19.2)	866	95 (11.0)	130	7 (5.4)
Hypercholesterolemia	-	-	148	70 (47.3)	866	301 (41.2)	-	-
History of smoking	277		151		866		130	
Current smoker		41 (14.8)		17 (11.3)		73 (8.4)		12 (9.2)
Ex-smoker		91 (32.5)		80 (53)		378 (43.6)		61 (46.9)
Never smoked		145 (51.8)		54 (35.8)		415 (47.9)		57 (43.8)
History of stroke			150	6 (4)	866	55 (6.4)	130	17 (13.1)
BMI, mean (SD)			151	28.7 (4.8)	866	27.9 (4.5)	124	27.4 (4.5)
Adult SES (manual)	274	60 (21.4)	151	62 (41.1)	850	176 (20.7)	130	81 (62.3)
Psychiatric measures								
QUIDS-16	279	3	-	-	-	-	-	-
HADS-D, median (IQR)	-	-	151	2	865	2 (3)	130	4

HADS-A, median (IQR)	279	3	151	4	865	4 (5)	130	5
Cognitive assessment								
Raven's matrices	280	8.41 (2.5)	-	-	-	-	-	-
AH4	-	-	149	24.3 (8.5)	-	-	-	-
MMSE	-	-	-	-	865	28.8 (1.4)	126	28.1 (1.7)

B

	STRADL		Dutch Famine		LBC1936		Simpsons	
Birth factors								
Maternal age, mean (SD)	-	-	151	27.8 (6.2)	176	27.9 (5.6)	130	27.7 (6.3)
Mother >35 years at birth	279	31 (11.1)	-	-	-	-	-	-
Mother not married at birth	279	4 (1.4)	151	24 (15.9)	-	-	130	15 (11.5)
Maternal weight (kg), mean (SD)	-	-	130	68.2 (9.0)	-	-	-	-
Birth weight (g), mean (SD)	-	-	151	3438.8 (488.0)	172	3323.2 (493.7)	130	3331.5 (461.7)
Low birth weight (<5.5 lbs)	279	9 (3.2)	-	-	-	-	-	-
Birth length (cm), mean (SD)	-	-	148	50.7 (2.0)	95	49.8 (3.3)	124	50.7 (2.7)
Ponderal index	-	-	148	26.3 (2.4)	95	27.3 (5.2)	124	25.7 (4.1)
Preterm	241	7 (2.9)	-	-	-	-	130	17 (13.1)
Head circumference (cm),mean (SD)	-	-	150	32.8 (1.5)	-	-	-	-
Head circumference to length ratio, mean (SD)	-	-	147	64.7 (2.9)	-	-	-	-
Head circumference to weight ratio, mean (SD)	-	-	150	9.7 (1.3)	-	-	-	-
Placental weight (g), mean (SD)	-	-	-	-	-	-	94	678.8 (146.3)
Placental volume (cm3), mean (SD)	-	-	125	707.4 (272.5)	-	-	-	-

Placental area (cm^2), mean (SD)	-	-	132	353.4 (91.8)	-	-	-	-
Placental to weight ratio	-	-	132	10.4 (2.3)	-	-	-	-
Famine exposure			151					
Exposed to famine				99 (65.6)				
Born before the famine	-	-		52 (34.4)	-	-	-	-
Exposed in early gestation	-	-		50 (33.1)	-	-	-	-
Preconceptional exposure	-	-		49 (32.5)	-	-	-	-
Childhood factors								
Childhood IQ	271	102.1 (9.5)	-	-	816	100.7 (15.32)	42	100.1 (14.8)
Premorbid IQ	280	31.7 (4.0)	-	-	864	34.4 (8.2)	130	29.5 (8.1)
Education								
Mean years of education	278	11.14 (1.1)	-	-	866	10.8 (1.1)	130	10.2 (2.1)
Low vs high level of education	278	179 (64.4)	151	91 (60.3)	866	628 (72.5)	130	107 (82.3)
No qualifications (vs O level and above)	278	34 (12.2)	-	-	864	153 (17.7)	-	-
Childhood SES								
Manual Father's occupation (vs non-manual)	265	181 (68.3)	123	83 (67.5)	788	579 (66.9)	130	91 (70.0)
Father's years of education, mean (SD)	-	-	-	-	674	10.0 (2.3)	-	-
Outdoor toilet	-	-	-	-	865	98 (11.3)	130	9 (6.9)
Number of people sharing a toilet, mean (SD)	-	-	-	-	860	5.3 (2.5)	130	5.6 (3.2)
Overcrowding index, mean (SD)	-	-	-	-	863	1.4 (0.8)	130	1.4 (0.7)

HADS-A: Hospital Anxiety and Depression Scale-anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale-depression subscale; QIDS: Quick Inventory of Depressive Symptoms; AH4: Alice Heim 4 test; MMSE: Mini Mental State Exam. NOTE: - is used where data are not available

6.3.2 Symptoms of depression

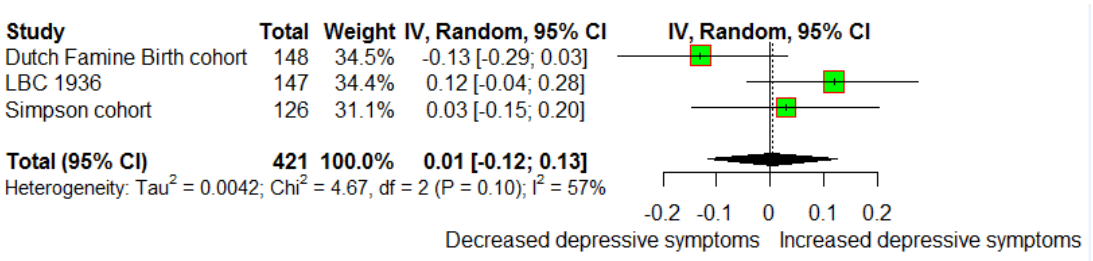
6.3.2.1 Birth factors and depressive symptoms

In the STRADL cohort having a mother who was not married at birth was associated with lower depressive symptoms on the QIDS-16 (β= -0.06, p=0.03). No other birth factors were associated with depressive symptoms on the QIDS-16 (table 6.2).

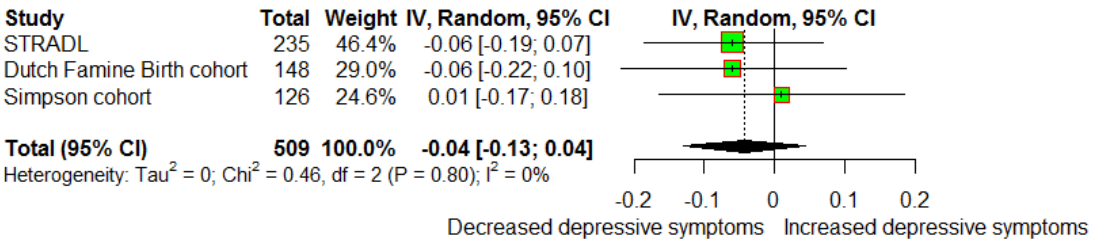
In the Dutch Famine Birth Cohort people exposed to famine scored higher on the HADS-D than those unexposed (β= 0.36, p=0.01, Table 6.2). When the exposed group with further divided those exposed in early gestation and those exposed to famine in preconception both scored higher on the HADS-D compared to those born before the famine who were not exposed in utero (β= 0.72, p=0.01; B=0.45, p=0.01). Tests for interaction between exposure groups and sex were non-significant (exposed in early gestation p=0.29; conceived after the famine p=0.07). In the LBC 1936 increasing ponderal index was associated with lower HADS-D scores (β= -0.24, p=0.03). No other birth factors were associated with HADS-D scores in any cohort (Table 6.2)

Birth factors and depressive symptoms: Meta-analysis of cohorts

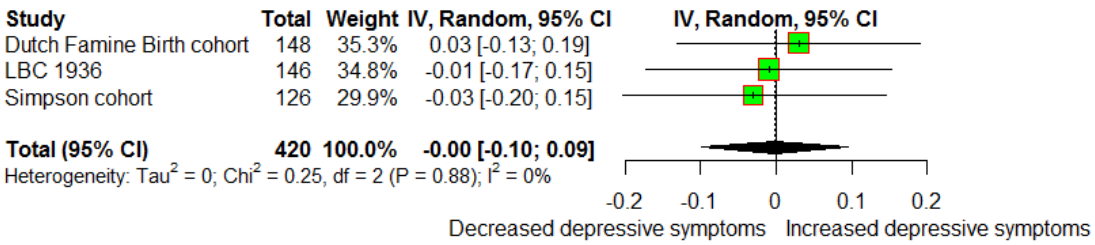
(A) Maternal age



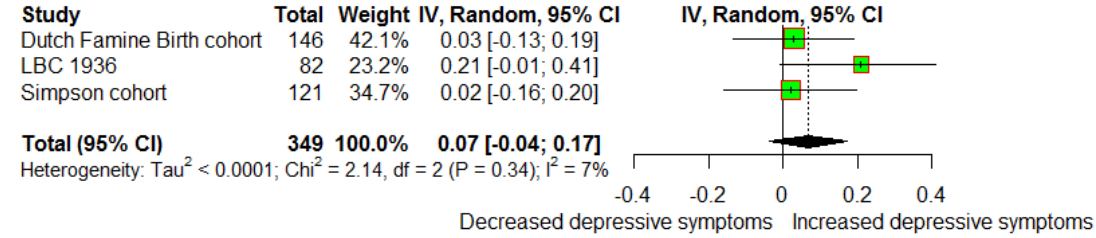
(B) Mother unmarried at birth



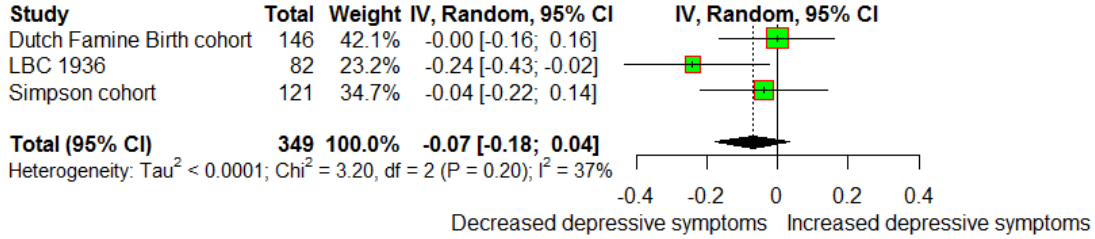
(C) Increasing birth weight



(D) Increasing birth length



(E) Increasing ponderal index



(F) Preterm

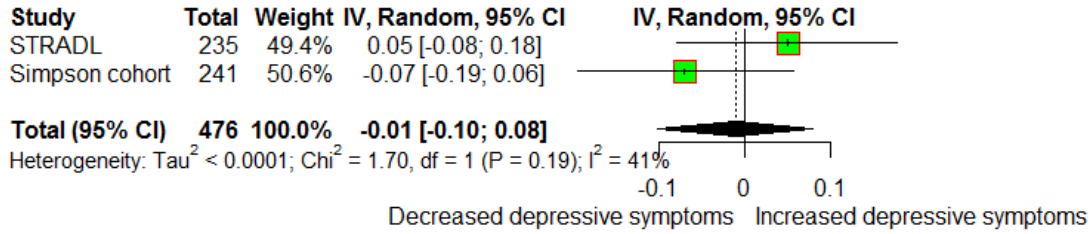


Figure 6.1 (A-F): Forest plots showing associations between birth factors and symptoms of anxiety on the HADS-D and the QIDS-16. Forest plots are presented for (A) maternal age (B) mother unmarried at birth (vs married) (C) birth weight (D) birth length (E) ponderal index (F) preterm (vs term). All analyses are adjusted for age, sex, hypertension, smoking behaviour, adult SES and cognition.

Table 6.2 Birth factors and depressive symptoms on the QIDS in the STRADL cohort and the HADS-D in the Dutch Famine Birth Cohort, the LBC 1936 and the Simpson cohort.

	STRADL			**Dutch famine**			**LBC36**			**Simpsons**		
	β	SE†	p	β	SE	p	β	SE	p	β	SE	p
	QIDS						**HADS-D**					
Maternal age	0.04*	0.87	0.61	-0.13	0.04	0.13	0.12	0.03	0.13	0.03	0.03	0.73
Mother not married at birth	**-0.06**	**0.18**	**0.03**	-0.06	0.90	0.55	-		-	0.01	0.76	0.94
Maternal weight (kg)	-	-	-	0.10	0.04	0.28	-		-	-	-	-
Birth weight (g)	-	-	-	0.03	0.06	0.72	-0.01	0.04	0.87	-0.03	0.05	0.74
Low birth weight (<5.5lbs)	0.02	1.92	0.85	-	-	-	-	-	-	-	-	-
Birth length (cm)	-	-	-	0.03	0.14	0.72	0.21	0.07	0.06	0.02	0.08	0.81
Ponderal index	-	-	-	-0.001	0.15	0.99	**-0.24**	**0.05**	**0.03**	-0.04	0.05	0.68
Preterm	0.05	2.29	0.60	-	-	-	-	-	-	-0.07	0.49	0.49
Head circumference (cm)	-	-	-	-0.01	0.23	0.95	-	-	-	-	-	-
Head circumference to length ratio	-	-	-	-0.03	0.08	0.65	-	-	-	-	-	-
Head circumference to weight ratio	-	-	-	-0.04	0.22	0.70	-	-	-	-	-	-
Placental weight (g)	-	-	-	-	-	-	-	-	-	-0.19	0.20	0.11
Placental volume	-	-	-	0.13	0.001	0.29	-	-	-	-	-	-
Placental area	-	-	-	-0.06	0.003	0.54	-	-	-	-	-	-
Placental to weight ratio	-	-	-	-0.11	0.15	0.31	-	-	-	-		-
Famine exposure												
Exposed to famine (vs unexposed)	-	-	-	**0.36**	**0.93**	**0.01**	-	-	-	-	-	-
Born before the famine	-	-	-	Reference			-	-	-	-	-	-
Exposed in early gestation	-	-	-	**0.72**	**1.70**	**0.01**	-	-	-	-	-	-
Preconceptional exposure	-	-	-	**0.45**	**1.01**	**0.01**	-	-	-	-	-	-

QIDS-16: Quick Inventory of Depressive Symptoms; HADS-D: Hospital Anxiety and Depression Scale; All analyses are adjusted for age, sex, hypertension, smoking behaviour, adult SES, cognition * Maternal age over the age of 35;. All betas are standardised. †SE is based on 1000 bootstrap samples

6.3.2.2 Childhood factors and depressive symptoms

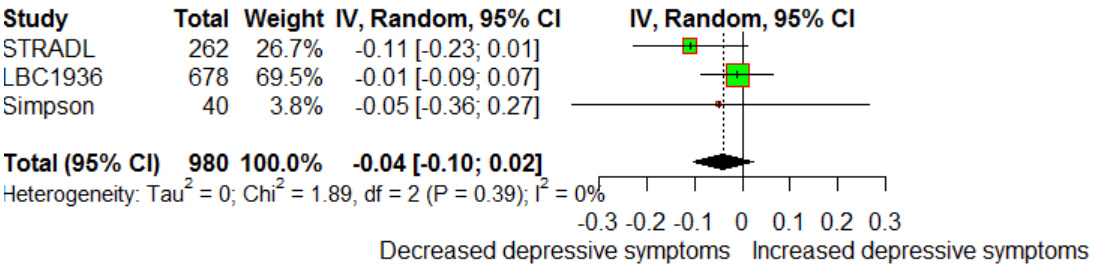
In the STRADL cohort more years of education were associated with decreased depressive symptoms on the QIDS-16 (β= -0.15, p=0.03, Table 6.3).

In the LBC 1936 having no qualifications (compared to at least O levels) was associated with higher HADS-D scores (β= 0.08, p=0.04). In the Dutch Famine Birth Cohort having a father with a manual occupation at birth was associated with higher depressive symptoms on the HADS (β= 0.02, p=0.03). In the LBC 1936 increasing number of people sharing a toilet were associated with higher HADS-D scores (β= 0.08, p=0.04). No childhood factors were associated with HADS-D scores in the Simpson cohort (Table 6.3)

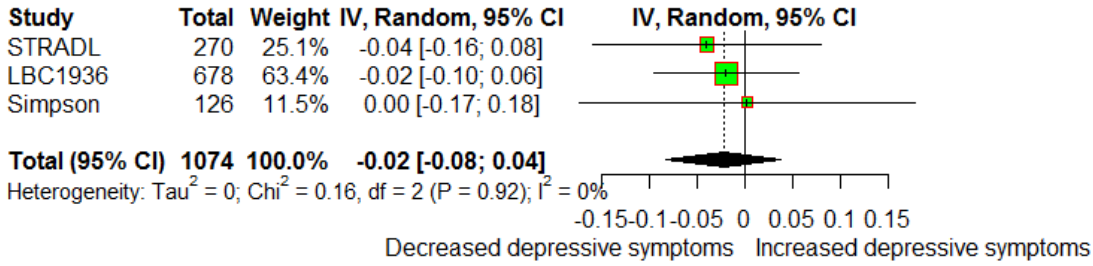
Childhood factors and depressive symptoms: Meta-analysis of cohorts

Across STRADL and the LBC 1936 having no qualifications was associated with increased depressive symptoms (β= 0.09, P=0.01, figure 6.2E). Across the LBC 1936 and Simpson cohort increasing number of people sharing a toilet was associated with increased depressive symptoms (β= 0.07, P=0.045, figure 6.2H).

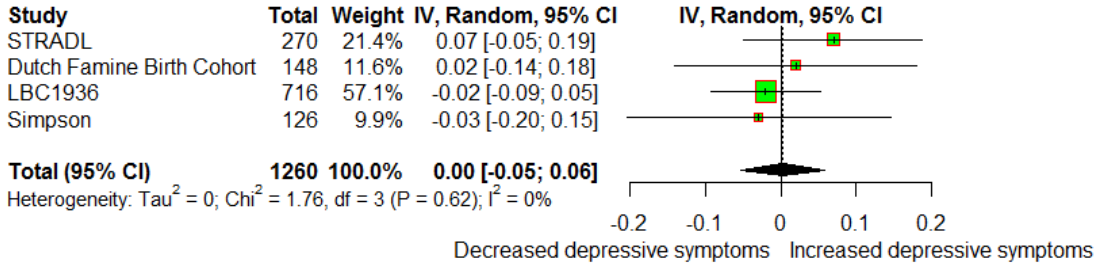
(A) Childhood IQ



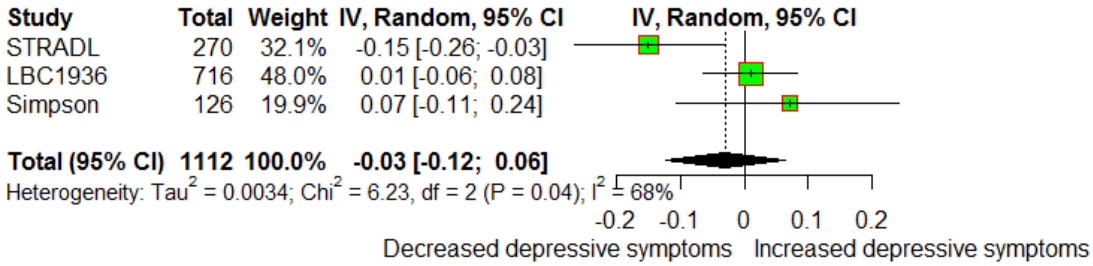
(B) Premorbid IQ



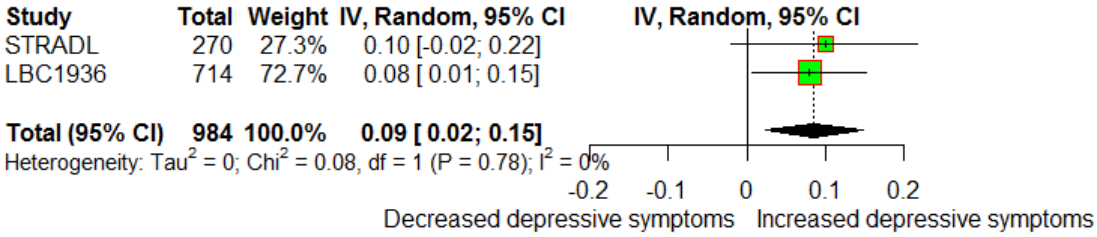
(C) Low education



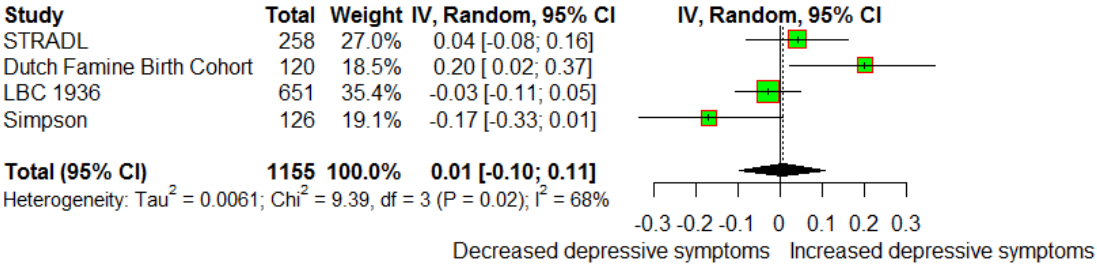
(D) Increasing years of education



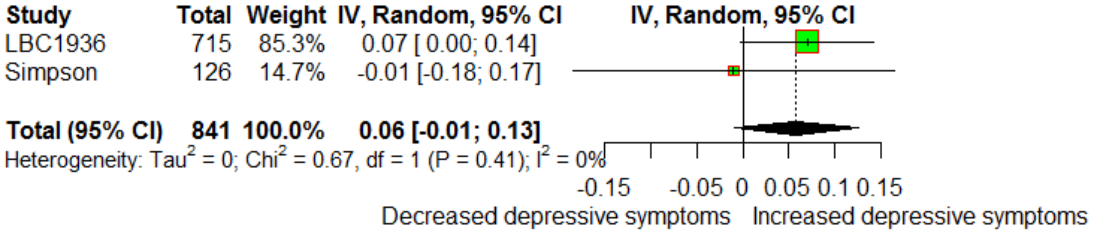
(E) No qualifications



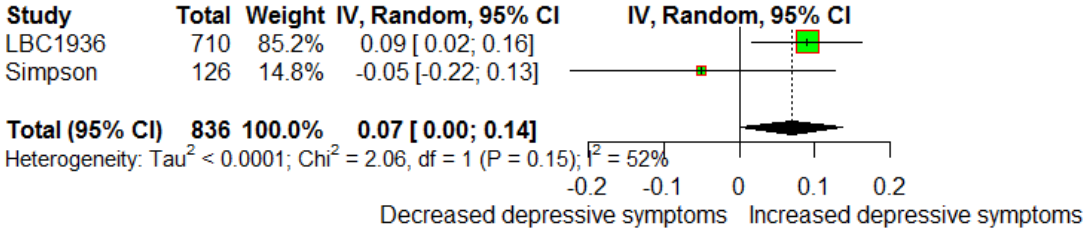
(F) Manual childhood SES



(G) Outdoor toilet



(H) Increasing number of people sharing a toilet



(I) Overcrowding index

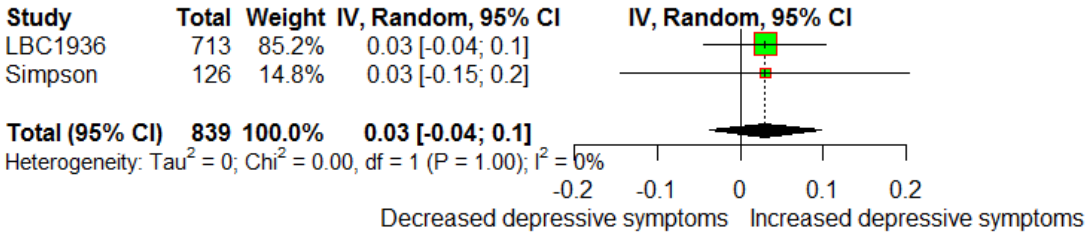


Figure 6.2: Forest plots showing associations between childhood factors and symptoms of depression on the QIDS-16 or HADS-D. Forest plots are presented for (A) childhood IQ (B) premorbid IQ (C) low education (D) years of education (E) No qualifications (vs o level and above) (F) manual childhood SES (vs non manual) (G) outdoor toilet (vs indoor toilet) (H) number of people sharing a toilet (I) overcrowding index.

All analyses are adjusted for age, sex, hypertension, smoking behaviour, adult SES and cognition.

Table 6.3 Childhood factors and depressive symptoms on the QUIDS-16 in the STRADL cohort and the HADS-D in the Dutch Famine Birth Cohort, the LBC 1936 and the Simpson cohort

	STRADL			Dutch famine			LBC36			Simpsons		
	β	SE†	p	β	SE†	p	β	SE†	p	β	SE†	p
	QUIDS-16						HADS-D					
Childhood IQ	-0.11	0.02	0.11	-	-	-	-0.01	0.01	0.86	-0.05	0.03	0.83
Premorbid IQ	-0.04	0.05	0.51	-	-	-	-0.02	0.01	0.64	0.002	0.03	0.99
Education												
Mean years of education	**-0.15**	**0.19**	**0.03**	-	-	-	0.01	0.08	0.78	0.07	0.11	0.51
Low education level	0.07	0.40	0.19	0.02	0.56	0.86	-0.02	0.18	0.58	-0.03	0.55	0.80
No qualifications	0.10	0.77	0.18	-	-	-	**0.08**	**0.21**	**0.04**	-	-	-
Childhood SES												
Manual father's occupation	0.04	0.40	0.53	**0.20**	**0.50**	**0.01**	-0.03	0.18	0.47	-0.17	0.47	0.08
Father's years of education	-	-	-	-	-	-	0.01	0.04	0.78	-	-	-
Outdoor toilet	-	-	-	-	-	-	0.07	0.32	0.14	-0.01	0.75	0.88
Number of people sharing a toilet	-	-	-	-	-	-	**0.09**	**0.04**	**0.03**	-0.05	0.06	0.53
Overcrowding index	-	-	-	-	-	-	0.03	0.12	0.44	0.03	0.28	0.75

QUIDS-16: Quick Inventory of Depressive Symptoms; HADS-D: Hospital Anxiety and Depression Scale; SES: socioeconomic status

All betas are standardised. †SE is based on 1000 bootstrap samples. All analyses are adjusted for age, sex, hypertension, smoking behaviour, adult SES, cognition

6.3.2.3 Multiple regression analyses: depressive symptoms

To assess the independence of associations between the early life factors and depressive symptoms a series of multiple regression analyses were conducted, adjusting for risk factors and other early life factors (Tables 6.4- 6.6).

Famine exposure and childhood SES

In the Dutch Famine Birth cohort the association between famine exposure and depressive symptoms remained statistically significant after adjustment for education and childhood SES (versus born before the famine: exposed in early gestation β= 0.72, p=0.003; preconceptional exposure β= 0.49, p= 0.01, Table 6.4). The association between low childhood SES and increased depressive symptoms was attenuated but remained statistically significant after adjustment for education and famine exposure (β= 0.19, p=0.03, Table 6.4). The number of risk factors included in the model was reduced in this analysis due to the small sample size.

Table 6.4: Multiple regression analysis of associations between famine exposure, education and childhood SES and depressive symptoms on the HADS-D in the Dutch Famine Birth cohort. Analysis is adjusted for each early life factor, age, sex, adult SES and current cognition

	Dutch Famine Birth cohort		
	β	SE	p
	HADS-D		
Born before the famine	Reference		
Exposed in early gestation	**0.72**	**1.50**	**0.003**
Preconceptual exposure	**0.49**	**1.09**	**0.01**
Low education	-0.03	0.58	0.79
Manual SES	**0.19**	**0.55**	**0.03**

All betas are standardised. SE is based on 1000 bootstrap samples

Education

In STRADL the association between increasing years of education and decreased depressive symptoms on the QIDS-16 lost statistical significance after adjustment for childhood SES and childhood IQ (β= -0.12, p=0.15, Table 6.5 A) or premorbid IQ (β= -0.14, p=0.06, Table 6.5 B).

Table 6.5 Multiple regression analysis of A) years of education, childhood IQ and childhood SES and depressive symptoms.in STRADL and the LBC 1936 and B) years of education, premorbid IQ and childhood SES and depressive symptoms in STRADL, the LBC 1936 and Simpson cohort All analyses adjusted for each early life factor in the table and age, sex, hypertension, smoking behaviour adult SES and current cognition.

A.

	STRADL			**LBC36**		
	β	SE	p	β	SE	p
	QIDS-16			**HADS-D**		
Years of education	-0.12	0.23	0.15	0.02	0.08	0.73
Childhood IQ	-0.05	0.03	0.53	-0.06	0.01	0.27
Manual SES	0.04	0.40	0.51	-0.03	0.19	0.50

NOTE: Mean years of education and childhood IQ were not available for the Dutch Famine Birth Cohort. The Simpson cohort is not include in this analysis due to the low number of participants with childhood IQ data.

B.

	STRADL			**LBC36**			**Simpsons**		
	β	SE	p	β	SE	p	β	SE	p
	QIDS-16			**HADS-D**					
Years of education	-0.14	0.21	0.06	0.02	0.08	0.61	0.03	0.11	0.78
Premorbid IQ	0.01	0.06	0.87	-0.04	0.01	0.40	-0.03	0.03	0.78
Manual SES	0.001	0.44	0.99	-0.03	0.19	0.49	-0.17	0.47	0.08

NOTE: Mean years of education and premorbid IQ were not available for the Dutch Famine Birth Cohort. All betas are standardised. SE is based on 1000 bootstrap samples

In the LBC 1936 associations between having no formal qualifications and increased depressive symptoms became non-significant after adjustment for childhood SES and childhood IQ (β= 0.07, p=0.09, Table 6.6 A) and premorbid IQ (β= 0.07, p=0.07, Table 6.6 B).

Table 6.6: Multiple regression analysis of A) Having no formal qualifications, childhood IQ and childhood SES and depressive symptoms in STRADL and the LBC 1936 B) Having no formal qualifications, premorbid IQ and childhood SES and depressive symptoms in STRADL and the LBC 1936 . All analyses adjusted for each early life factor in the table and age, sex, hypertension, smoking behaviour adult SES and current cognition.

A)

	STRADL			**LBC36**		
	β	SE	p	β	SE	p
	QIDS-16			**HADS-D**		
No qualifications	0.12	0.92	0.19	0.07	0.23	0.09
Childhood IQ	-0.05	0.02	0.49	-0.04	0.01	0.46
Manual SES	0.06	0.37	0.28	-0.03	0.19	0.38

NOTE: Data on qualifications were not available for the Dutch Famine Birth Cohort or the Simpson cohort

B)

	STRADL			**LBC36**		
	β	SE	p	β	SE	p
	QIDS-16			**HADS-D**		
No qualifications	0.13	0.87	0.13	0.07	0.24	0.07
Premorbid IQ	0.01	0.06	0.91	-0.01	0.01	0.79
Manual SES	0.03	0.41	0.65	-0.03	0.18	0.36

NOTE: Data on qualifications were not available for the Dutch Famine Birth Cohort or the Simpson cohort. All betas are standardised. SE is based on 1000 bootstrap samples.

6.3.1 Symptoms of anxiety

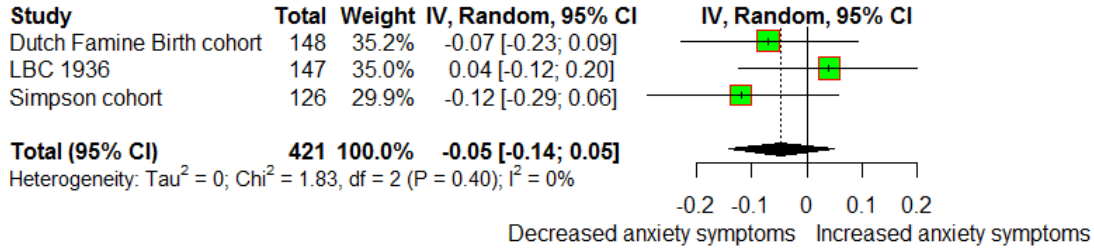
6.3.1.1 Birth factors and HADS-A

In the Dutch Famine Birth Cohort people exposed to famine scored higher on the HADS-A than those unexposed (β= 0.30, p=0.049, Table 6.7). When the exposed group was further divided those exposed in early gestation and those exposed to famine in preconception both scored higher on the HADS-A (β= 0.45, p=0.04; β= 0.33, p=0.03) compared to those born before the famine who weren't exposed. Tests for interaction between exposure groups and sex were non-significant (exposed in early gestation p=0.58; conceived after the famine p=0.99). No other birth factors were associated with scores on the HADS-A (Table 6.7).

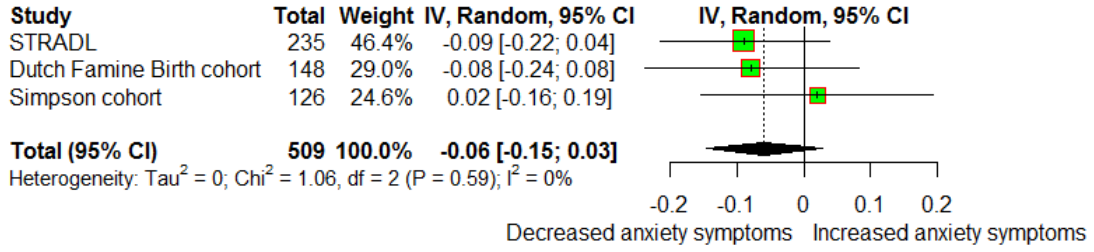
Birth factors and HADS-A: Meta-analysis of cohorts

Birth factors were not associated with symptoms of anxiety on the HADS-A in the meta-analysis (figure 6.3 A-F)

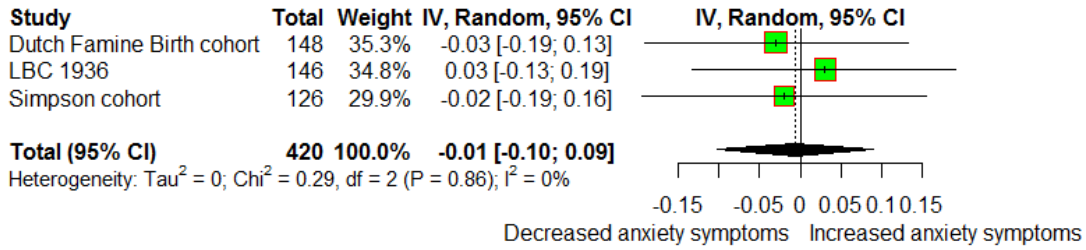
(A) Maternal age



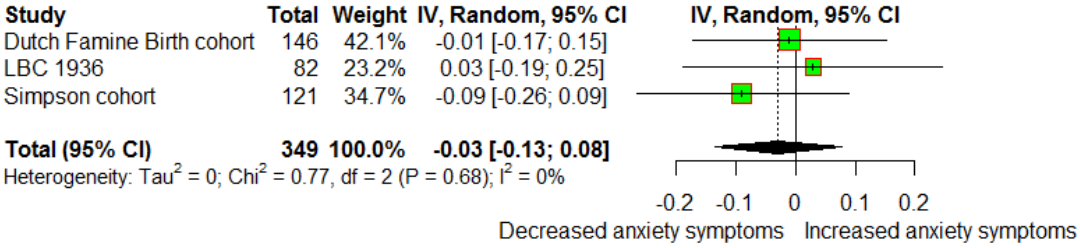
(B) Mother unmarried at birth



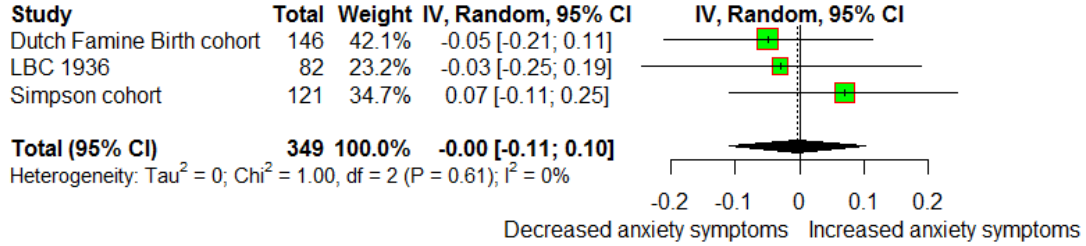
(C) Increasing birth weight



(D) Increasing birth length



(E) Increasing ponderal index



(F) Preterm

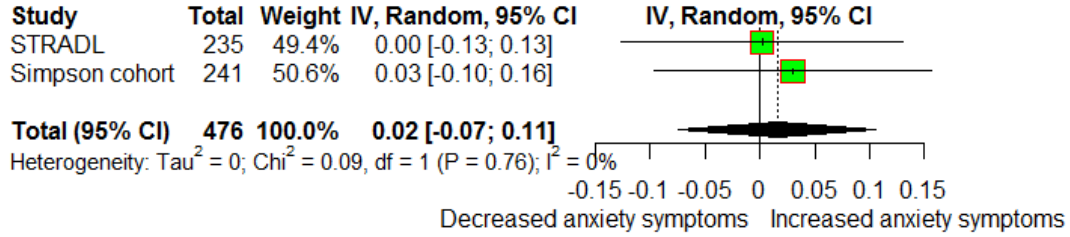


Figure 6.3 (A-F): Forest plots showing associations between birth factors and symptoms of anxiety on the HADS-A. Forest plots are presented for (A) maternal age (B) mother unmarried at birth (vs married) (C) birth weight (D) birth length (E) ponderal index (F) preterm (vs term).

Table 6.7 Birth factors and scores on the HADS-A in the STRADL cohort, the Dutch Famine Birth Cohort, the LBC 1936 and the Simpson cohort.

	STRADL			**Dutch famine**			**LBC36**			**Simpsons**		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Maternal age	-0.06*	0.61	0.33	-0.07	0.04	0.40	0.04	0.04	0.62	-0.12	0.05	0.25
Mother not married at birth	-0.09	1.65	0.19	-0.08	0.66	0.34	-	-	-	0.02	0.94	0.84
Maternal weight (kg)	-	-	-	0.05	0.03	0.58	-	-	-	-		-
Birth weight (per 100g)	-	-	-	-0.03	0.05	0.73	0.03	0.05	0.74	-0.02	0.07	0.85
Low birth weight (<5.5lbs)	-0.07	1.24	0.33	-	-	-	-	-	-	-	-	-
Birth length (cm)	-	-	-	-0.01	0.13	0.96	0.03	0.11	0.81	-0.09	0.12	0.35
Ponderal index	-	-	-	-0.05	0.11	0.57	-0.03	0.07	0.82	0.07	0.08	0.49
Preterm	0.002	1.50	0.98	-	-	-	-	-	-	0.03	0.89	0.78
Head circumference (cm)	-	-	-	0.04	0.17	0.62	-	-	-	-	-	-
Head circumference to length ratio	-	-	-	0.04	0.09	0.60	-	-	-	-	-	-
Head circumference to weight ratio	-	-	-	0.04	0.19	0.62	-	-	-	-	-	-
Placental weight (g)	-	-	-	-	-	-	-	-	-	-0.16	0.25	0.15
Placental volume	-	-	-	0.06	0.001	0.51	-	-	-	-	-	-
Placental area	-	-	-	-0.07	0.003	0.34	-	-	-	-	-	-
Placental to weight ratio	-	-	-	-0.10	0.11	0.25	-	-	-	-	-	-
Famine exposure												
Exposed to famine (vs unexposed)	-	-	-	**0.30**	**0.96**	**0.049**	-	-	-	-	-	-
Born before the famine	-	-	-	Reference			-	-	-	-	-	-
Exposed in early gestation	-	-	-	**0.45**	**1.42**	**0.04**	-	-	-	-	-	-
Preconceptional exposure	-	-	-	**0.33**	**1.01**	**0.03**	-	-	-	-	-	-

* Maternal age over the age of 35; NOTE: - is used where data are not available. All betas are standardised. Analyses adjusted for age, sex, hypertension, smoking behaviour, adult SES, cognition

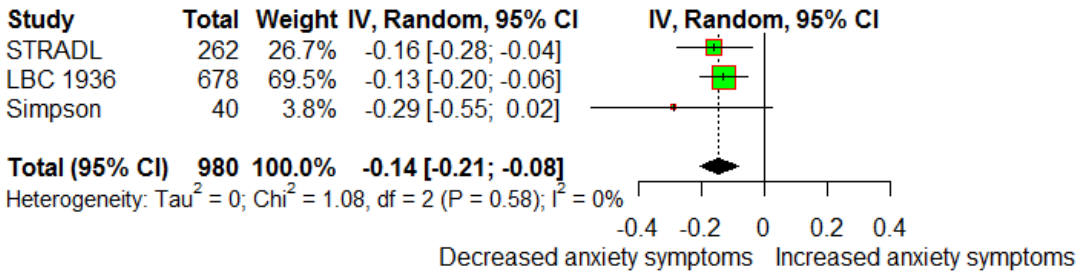
6.3.1.2 Childhood factors and HADS-A

In the STRADL cohort and LBC 1936 increasing childhood IQ was associated with lower HADS-A scores (β= -0.16, p=0.02; β= - 0.13, p=0.003). In the LBC 1936 having no qualifications (compared to at least O levels) was associated with higher HADS-A scores (β= 0.08, p=0.02). Increasing number of people sharing a toilet was associated with increased HADS-A scores (β=0.10, p=0.004). No childhood factors were associated with HADS-A scores in the Dutch Famine Birth cohort or the Simpson cohort (Table 6.8).

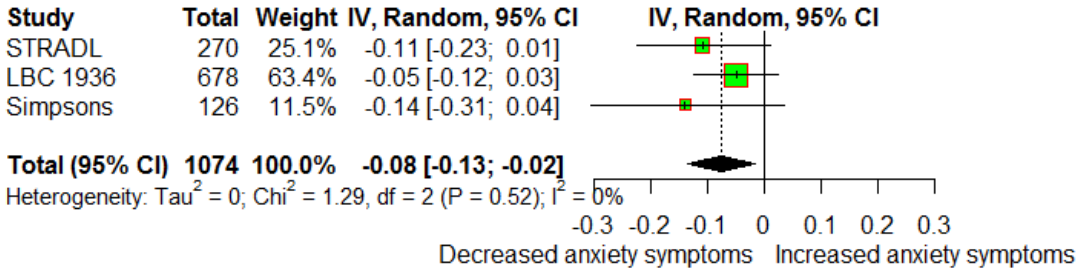
Meta-analysis of cohorts

Increasing childhood IQ and premorbid IQ were associated with decreased symptoms of anxiety across STRADL, the LBC 1936 and the Simpson cohort (β= -0.14, p<0.0001; β= -0.14, p<0.0001, Figures 6.4A-B). Having no qualifications was associated with increased symptoms of anxiety (β= 0.08, p=0.01, Figure 6.4E). Having an outdoor toilet and number of people sharing a toilet were associated with increased symptoms of anxiety (β= 0.18, P<0.001; β=0.08, p=0.02, Figure 6.4G).

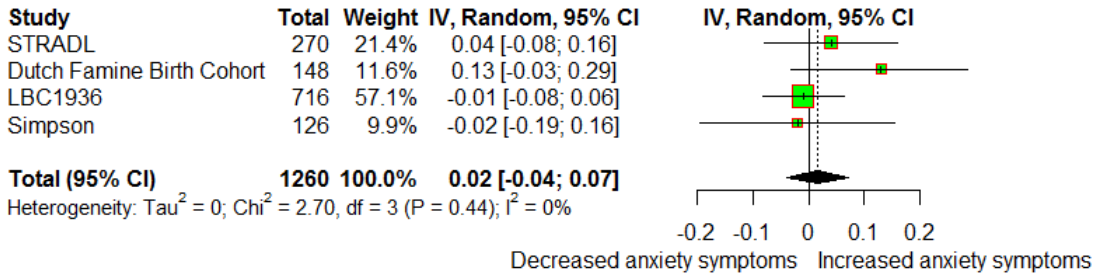
(A) Childhood IQ



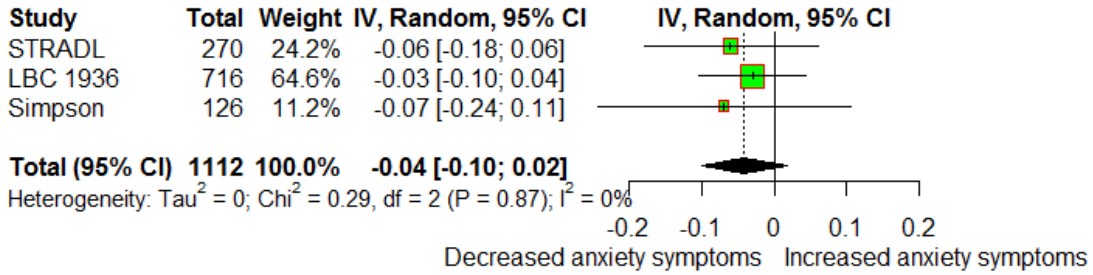
(B) Premorbid IQ



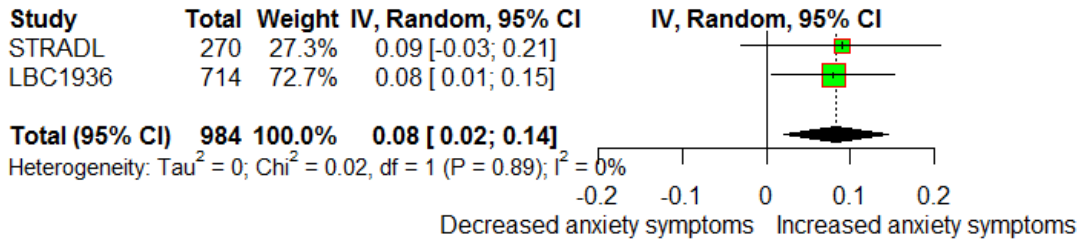
(C) Low education



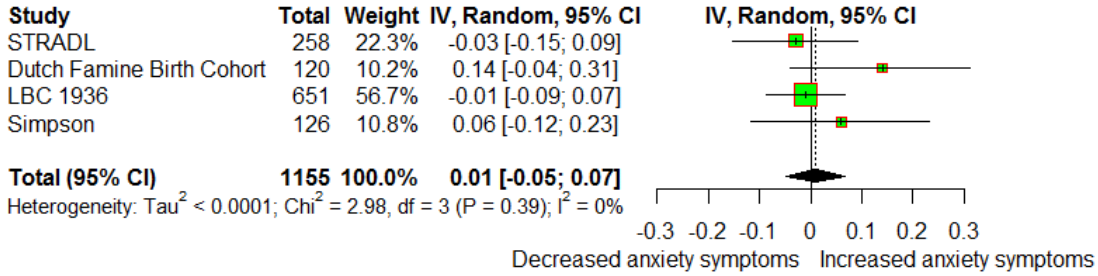
(D) Increasing years of education



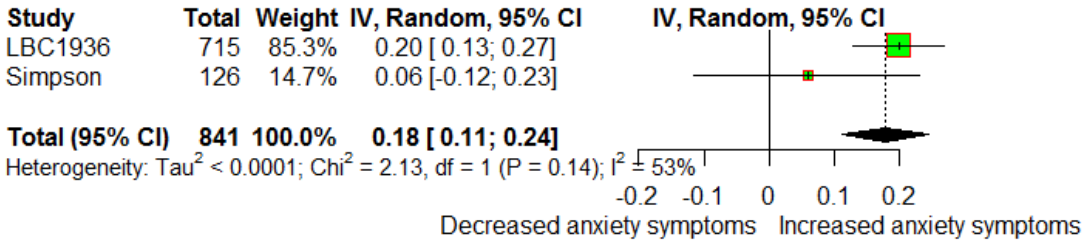
(E) No qualifications



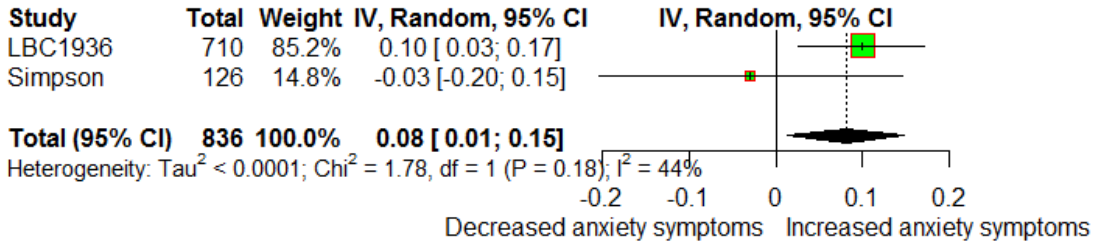
(F) Manual childhood SES



(G) Outdoor toilet



(H) Number of people sharing a toilet



(I) Overcrowding index

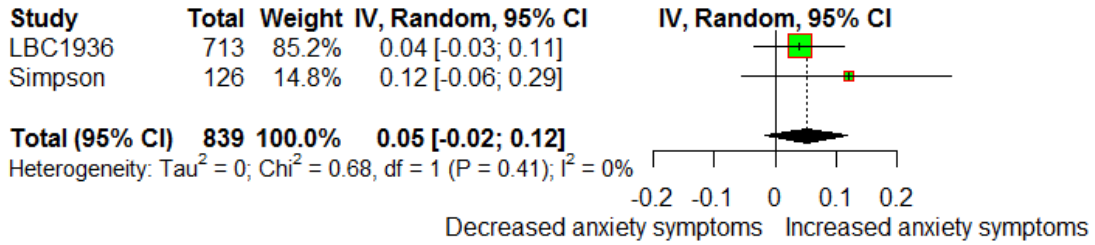


Figure 6.4 (A-H): Forest plots showing associations between childhood factors and symptoms of anxiety on the HADS-A. Forest plots are presented for (A) childhood IQ (B) premorbid IQ (C) low education (D) years of education (E) no qualifications (vs o level and above) (F) manual childhood SES (vs non manual) (G) outdoor toilet (vs indoor toilet) (H) number of people sharing a toilet (I) overcrowding index

All analyses are adjusted for age, sex, hypertension, smoking behaviour, adult SES and cognition.

Table 6.8 Childhood factors and scores the HADS anxiety subscale in STRADL, the Dutch Famine Birth Cohort, the LBC 1936 and the Simpson cohort.

	STRADL			Dutch famine			LBC36			Simpsons		
	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Childhood IQ	**-0.16**	**0.02**	**0.02**	-	-	-	**-0.13**	**0.01**	**0.003**	-0.29	0.04	0.13
Premorbid IQ	-0.11	0.05	0.10	-	-	-	-0.05	0.02	0.20	-0.14	0.04	0.17
Education												
Mean years of education	-0.06	0.18	0.39	-	-	-	-0.03	0.10	0.46	-0.07	0.15	0.50
Low education level	0.04	0.40	0.56	0.13	0.53	0.14	-0.01	0.25	0.70	-0.02	0.85	0.88
No qualifications (vs O level and above)	0.09	0.6	0.17	-	-	-	**0.08**	**0.29**	**0.02**	-		-
Childhood SES												
Manual father's occupation	-0.03	0.41	0.66	0.14	0.56	0.11	-0.01	0.26	0.87	0.06	0.66	0.49
Father's years of education	-	-	-	-	-	-	-0.04	0.05	0.34	-	-	-
Outdoor toilet	-	-	-	-	-	-	0.20	0.33	0.60	0.06	1.17	0.51
Number of people sharing a toilet	-	-	-	-	-	-	**0.10**	**0.04**	**0.004**	-0.03	0.09	0.73
Overcrowding index	-	-	-	-	-	-	0.04	0.15	0.27	0.12	0.44	0.19

All betas are standardised. All analyses are adjusted for age, sex, hypertension, smoking behaviour, adult SES, cognition

6.3.1.3 Multiple regression analysis HADS-A

Famine exposure

To assess the independence of associations between the early life factors and symptoms of anxiety a series of multiple regression analyses were conducted, adjusting for risk factors and other early life factors (Tables 6.9- 6.11).

In the Dutch Famine Birth Cohort the association between famine exposure and increased symptoms of anxiety remained statistically significant after education and childhood SES were added to the model (versus born before the famine: exposed in early gestation β= 0.54, p=0.02; preconceptional exposure β= 0.38, p=0.03, table 6.9). The number of risk factors included in the model was reduced in this analysis due to the small sample size of each famine exposure group.

Table 6.9 Multiple regression analysis of associations between famine exposure, education and childhood SES and symptoms of anxiety on the HADS-A in the Dutch Famine Birth cohort. The analysis is adjusted for each early life factor, age, sex, adult SES and current cognition

	Dutch Famine Birth cohort		
	β	SE	p
	HADS-A		
Born before the famine	Reference		
Exposed in early gestation	**0.54**	**1.47**	**0.02**
Preconceptional exposure	**0.38**	**1.07**	**0.03**
Low education	0.15	0.57	0.12
Manual SES	0.15	0.54	0.07

All betas are standardised

Childhood IQ

Associations between increasing childhood IQ and decreased symptoms of anxiety on the HADS-A remained statistically significant after adjustment for age, sex, hypertension, smoking behaviour, adult SES, cognition, mean years of education and childhood SES in STRADL (β= -0.17, p=0.02) and the LBC 1936 (β= -0.13, p=0.002) (Table 6.10). It was not possible to include the Simpson cohort in this analysis due to the small number of participants with childhood IQ scores.

Table 6.10 Multiple regression analysis of education, childhood IQ and childhood SES and symptoms of anxiety on the HADS-A in STRADL and the LBC 1936. The analyses is adjusted for each early life factor in the table and age, sex, hypertension, smoking behaviour adult SES and current cognition.

	STRADL			**LBC36**		
	β	SE	p	β	SE	p
	HADS-A					
Childhood IQ	**-0.17**	**0.02**	**0.02**	**-0.13**	**0.01**	**0.002**
Mean years of education	0.01	0.20	0.9	0.03	0.12	0.50
Manual SES	-0.06	0.43	0.4	-0.004	0.27	0.93

NOTE: the Simpson cohort is not included in this analyses due to low sample size. All betas are standardised.

Educational attainment

In the LBC 1936 associations between having no formal qualifications and increased symptoms of anxiety on the HADS-A became non-significant after adjustment age, sex, hypertension, smoking behaviour, adult SES, current cognition, childhood SES and childhood IQ (β= 0.06, p=0.10, Table 6.11A) and premorbid IQ (β= 0.06, p=0.10, Table 6.6B). In STRADL after adjustment for having no qualifications and childhood SES, increasing premorbid IQ was associated with lower symptoms of anxiety on the HADS-A (β= -0.17, p=0.01) (Table 6.11B).

Table 6.11: Multiple regression analysis of A) Having no formal qualifications, childhood IQ and childhood SES in STRADL and the LBC 1936 B) Having no formal qualifications, premorbid IQ and childhood SES in STRADL and the LBC 1936. All analyses adjusted for each early life factor in the table and age, sex, hypertension, smoking behaviour adult SES and current cognition.

A)

	STRADL			LBC36		
	β	SE	p	β	SE	p
	HADS-A					
No qualifications	0.08	0.62	0.20	0.06	0.31	0.10
Childhood IQ	-0.13	0.02	0.04	**-0.10**	**0.01**	**0.02**
Manual SES	-0.003	0.40	0.96	-0.03	0.26	0.47

B)

	STRADL			LBC36		
	β	SE	p	β	SE	p
	HADS-A					
No qualifications	0.11	0.58	0.06	0.06	0.32	0.10
Premorbid IQ	**-0.17**	**0.05**	**0.01**	-0.04	0.02	0.41
Manual SES	0.01	0.39	0.90	-0.01	0.26	0.72

NOTE: Data on qualifications obtained were not available for the Dutch Famine Birth cohort or Simpson cohort. All betas are standardised

6.3.3 Sensitivity analysis

A series of sensitivity analyses were conducted on the LBC 1936 to examine associations between early life factors and HADS scores taken at different waves; wave 1 when participants were approximately 69.5 years, wave 2 when they were approximately 72.5 years and wave 3 when they were approximately 76.3 years. For this analysis only participants who participated in all 3 waves of testing were included.

6.3.3.2 HADS-D

No birth factors were associated with HADS-D scores at wave 1 or wave 3 (table 6.12 A).

At wave 1 having no qualifications was and Increasing number of people sharing a toilet were associated with higher HADS-D scores (β= 0.08, p=0.02; β= 0.10, p=0.02, table 6.12 B).

At wave 3 increasing childhood and premorbid IQ were associated with lower HADS-D scores (β= -0.11, p=0.03; β= -0.15, p=0.002). Having no qualifications was associated with higher HADS-D scores (β= 0.10, p=0.01) (table 6.12 B)

6.3.3.1 HADS-A

Birth factors were not associated with HADS-A scores at wave 1 or wave 3 but the direction of effect was the same as for wave 2 (table 6.13 A).

At wave 1 increasing childhood and premorbid IQ were associated with lower HADS-A scores (β= -0.12, p=0.001; β= -0.07, 0.048). Number of people sharing a toilet was associated with increased HADS-A scores p= 0.12, p=<0.001, table 6.13 B).

At wave 3 increasing childhood and premorbid IQ were associated with lower HADS-A scores (β= -0.17, p=<0.001; β= -0.16, p<0.001). Having no qualifications was associated with higher HADS-A scores (β= 0.13, p=0.001). Increasing Father's years of education was associated with decreased HADS-A scores (β= -0.10, p=0.02). Number of people sharing a toilet was associated with increased HADS-A scores (β= 0.13, p=0.001, table 6.13 B).

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Table 6.12 Sensitivity analysis: (A) birth and (B) childhood factors and scores on the HADS-D in the LBC 1936 waves 1-3

A.

	Wave 1 (n=225)			**Wave 2 (n=148)**			**Wave 3 (n=145)**		
	β	**SE**	**p**	β	**SE**	**p**	β	**SE**	**p**
Maternal age	-0.01	0.03	0.81	0.08	0.04	0.35	0.05	0.03	0.45
Birth weight (per 100g)	0.05	0.04	0.45	0.001	0.04	0.99	-0.11	0.05	0.24
Birth length (cm)	0.18	0.06	0.06	0.19	0.09	0.11	-0.03	0.09	0.82
Ponderal index	-0.11	0.04	0.18	**-0.24**	**0.05**	**0.03**	-0.11	0.05	0.29

B.

	Wave 1 (n= 1067)			**Wave 2 (n=866)**			**Wave 3 (n=683)**		
	β	**SE**	**p**	β	**SE**	**p**	β	**SE**	**p**
Childhood IQ	-0.06	0.01	0.14	-0.01	0.01	0.86	**-0.11**	**0.01**	**0.03**
Premorbid IQ	-0.06	0.01	0.10	-0.02	0.01	0.64	**-0.15**	**0.01**	**0.002**
Education									
Mean years of education	-0.04	0.06	0.24	0.01	0.08	0.78	-0.04	0.08	0.29
Low education level	0.03	0.15	0.29	-0.02	0.18	0.58	0.01	0.19	0.81
No qualifications (vs O level and above)	**0.08**	**0.21**	**0.02**	**0.08**	**0.21**	**0.04**	**0.10**	**0.28**	**0.01**
Childhood SES									
Manual Father's occupation	-0.03	0.17	0.45	-0.03	0.18	0.47	-0.01	0.21	0.79
Father's years of education	-0.01	0.04	0.71	0.01	0.04	0.78	-0.08	0.05	0.05
Outdoor toilet (vs indoor toilet)	0.02	0.21	0.48	0.07	0.32	0.14	0.01	0.27	0.89
Number of people sharing a toilet	**0.10**	**0.03**	**0.01**	**0.09**	**0.04**	**0.03**	0.07	0.04	0.09
Overcrowding index	0.05	0.09	0.12	0.03	0.12	0.44	0.04	0.12	0.31

All betas are standardised. All analyses adjusted for age, sex, hypertension, smoking behaviour, adult SES, cognition.SE is based on 1000 bootstrap samples

Table 6.13: Sensitivity analysis: (A) birth and (B) childhood factors and scores on the HADS-A in the LBC 1936 waves 1-3

A.

	WAVE 1 (n=225)			WAVE 2 (n=148)			WAVE 3 (n=145)		
	β	SE	p	β	SE	p	β	SE	p
Maternal age	0.02	0.04	0.73	0.01	0.05	0.87	0.14	0.05	0.09
Birth weight (per 100g)	-0.03	0.04	0.67	0.02	0.05	0.77	-0.11	0.05	0.18
Birth length (cm)	-0.02	0.09	0.80	-0.02	0.10	0.98	-0.12	0.11	0.27
Ponderal index	0.003	0.06	0.97	-0.03	0.07	0.82	-0.04	0.07	0.77

B.

	Wave 1 (n=1067)			Wave 2 (n=866)			Wave 3 (n=683)		
	β	SE	p	β	SE	p	β	SE	p
Childhood IQ	**-0.12**	**0.01**	**0.001**	**-0.12**	**0.01**	**0.003**	**-0.17**	**0.01**	**<0.001**
Premorbid IQ	**-0.07**	**0.01**	**0.048**	-0.05	0.02	0.20	**-0.16**	**0.02**	**<0.001**
Education									
Mean years of education	-0.04	0.09	0.18	-0.03	0.10	0.46	**-0.10**	**0.11**	**0.01**
Low education level	0.04	0.23	0.24	-0.01	0.25	0.70	0.07	0.28	0.10
No qualifications (vs O level and above)	0.04	0.26	0.21	**0.08**	**0.29**	**0.02**	**0.13**	**0.31**	**0.001**
Childhood SES									
Manual Father's occupation	-0.004	0.23	0.89	-0.01	0.26	0.87	0.00	0.28	0.997
Father's years of education	-0.04	0.05	0.24	-0.04	0.05	0.34	**-0.10**	**0.06**	**0.02**
Outdoor toilet	0.03	0.30	0.33	0.20	0.33	0.60	0.03	0.37	0.36
No. of people sharing a toilet	**0.12**	**0.04**	**<0.001**	**0.10**	**0.04**	**0.004**	**0.13**	**0.05**	**0.001**
Overcrowding index	0.05	0.13	0.09	0.04	0.15	0.27	0.04	0.15	0.30

All betas are standardised. All analyses are adjusted for age, sex, hypertension, smoking behaviour, adult SES, cognition

6.4 Discussion

6.4.1 Summary of findings

This study is one of the first to examine multiple early life influences on symptoms of anxiety and depression in older adults using data collected at birth and 62-78 years later. The current findings from four cohorts supports previous research suggesting that some early life factors may increase psychiatric symptoms of depression and anxiety in later life independent of common risk factors. In the Dutch Famine Birth Cohort those exposed to famine during gestation had higher symptoms of depression and anxiety at age 68 than those not exposed. When the exposed group was divided into those exposed in early gestation and those exposed preconceptionally both groups had more symptoms of depression and anxiety than those born before the famine. This association was independent of education level and childhood SES.

In childhood, higher IQ and more education appears to be protective against symptoms of anxiety and depression. In STRADL and LBC 1936 increasing childhood IQ was associated with lower symptoms of anxiety independent of vascular risk factors, current cognition, adult and childhood SES and education. On the other hand, the protective effect of increasing years of education (STRADL) and the harmful effect of low educational attainment (LBC 1936) lost statistical significance after adjustment for childhood or premorbid IQ and childhood SES. This suggests that the association between education and symptoms of anxiety and depression are independent of adult factors such as SES and cognition but may be mediated by other early life factors. Measures of childhood SES were also associated with symptoms of depression and anxiety in the LBC 1936 and Dutch Famine Birth Cohort. This included low SES and more depressive symptoms in the Dutch Famine Birth cohort which was independent of education and famine exposure.

6.4.2 Birth factors and HADS

A range of factors including women's nutrition just before conception or during early pregnancy may play an important role in pregnancy outcomes and the health of the offspring by affecting critical developmental processes that begin early in pregnancy (Ramakrishnan et al., 2012). Poor nutrition during gestation may cause changes to the neuroendocrine system producing lifelong effects on neurodevelopment and increasing later vulnerability to depression and anxiety (Thompson et al., 2001). The

present findings provide support for an association between exposure to prenatal famine and symptoms of anxiety and depression in adulthood. These findings are consistent with previous research in the Dutch Famine Birth cohort. de Rooij and colleagues found that men, but not women, exposed to famine in early gestation had higher symptoms of depression on the HADS-D, were more likely to report a past diagnosis of depression by a doctor and had a higher incidence of moderate to severe symptoms of anxiety, defined as a score of 8 and above on the HADS-A (de Rooij et al., 2011). In contrast, two studies by Brown and colleagues (Brown et al., 1995, Brown et al., 2000) found that those exposed to famine in mid and late gestation were more likely to be hospitalised for affective disorder than unexposed individuals. They found no association between exposure in early gestation and hospitalisation. However, the fact that the outcome in Brown's studies was hospitalisation for affective disorders, rather than self-reported symptoms of depression and anxiety as examined here, may explain the different findings. Only individuals with the most severe forms of affective disorders are hospitalised and therefore do not represent milder symptoms commonly seen in community dwelling older adults or the population as a whole. Furthermore, participants in Brown's studies were much younger (aged 33-51 years) than those in the present study. Late-life depression and depressive symptoms (after the age of 60) are different to depression seen in early or mid-life and often arise in the context of medical and neurologic disorders such dementia and cerebrovascular disease (Alexopoulos, 2005). The timing of maternal nutrient restriction has a major influence on which foetal organs and systems are thought to be affected. It may be that these different forms of depression may be programmed during different stages of gestation.

The results presented here suggest that in addition to nutrition during pregnancy the mother's nutritional health during the preconception period may also be critical to the development of the foetus. Susser and colleagues describe the height of the Dutch famine as occurring when the effects of famine on morbidity and mortality were most severe which was between February and April 1945 (Susser et al., 1996). Many of the members of the preconceptional famine exposure group in this chapter would have been conceived during this time. They were therefore likely to have been exposed (though for less than 13 weeks) to the height of the famine around the time of conception or in very early gestation. The finding that these participants had higher scores of anxiety and depression compared to those born before the start of the famine, is consistent with previous research which has found higher levels of self-

reported depressive symptoms and lower quality of life scores in this group (Stein et al., 2009). However the effect sizes in this analysis were relatively small and famine exposure only explained 4.3% and 15.4% of the variance in symptoms of depression and anxiety respectively. Therefore although early life factors may have some influence, later life factors and genetics likely have a larger impact.

6.4.3 Childhood factors and HADS

Previous research examining associations between childhood factors and later depression and anxiety has mainly been conducted in those in early adulthood or mid-life. Furthermore studies in both adulthood and later life tend to focus on depression rather than anxiety. Reasons for this are unclear but it is possibly due to the fact that symptoms of anxiety in older adults often overlap with symptoms of physical disorders and depression which make it difficult to identify.

Meta-analysis of 29 longitudinal studies including 121,749 individuals under the age of 65, found that higher childhood IQ was associated with lower risk of subsequent major depression (Scult et al., 2017). Similar findings have been reported in cross sectional studies. For example, in the largest study to examine childhood IQ and mental health, Gale and colleagues followed up over 1 million male Swedish conscripts at age ~37 who had completed cognitive testing aged 18. They found that each standard deviation decrease in cognitive ability was associated with a 50% increased risk of being admitted to hospital for mood disorders (Gale et al., 2010). These observations have also been reported for depression in middle age (Wraw et al., 2016, Osler et al., 2015). There have been no published meta-analyses of associations between childhood IQ and later anxiety. However, several previous individual studies have reported an association between higher childhood cognitive ability and lower later risk of psychological distress and generalised anxiety disorder (GAD) in young adulthood (Martin et al., 2007, Koenen et al., 2009, Gale et al., 2008) and across the life course (Erickson et al., 2016). These studies of childhood cognitive ability and later depression and anxiety have focused mainly on clinical diagnoses and hospital admissions for major depression or GAD. One study found that each standard deviation increase in childhood IQ was associated with a 26% reduced risk of a diagnosis of anxiety disorder in adulthood (Koenen et al., 2009). The few studies which have examined childhood cognitive ability and psychological health in older adults have focused more on symptoms of depression and anxiety, rather than clinical diagnosis, consistent with the methodology in this chapter. Meta-analysis of data from

four cohort studies, including the Aberdeen Birth Cohort and the LBC 1921, found that higher prior intelligence was associated with reduced odds of depression and anxiety, defined as scoring 8 or more on the each HADS subscale, at ages 64-79 (Gale et al., 2011). Previous research in the LBC 1936 at wave 1 found that age 11 IQ was negatively correlated with symptoms of depression and anxiety on the HADS (Brett et al., 2012). Results from the sensitivity analysis presented in this chapter shows that these wave 1 associations remain after adjustment for vascular risk factors, adult SES and current cognition. Studies of other cohorts have reported mixed findings. In the LBC 1921 there were significant associations between age 11 IQ and HADS-A but not HADS-D, consistent with the main analysis of age 11 IQ and HADS in this chapter (Brett et al., 2012). However a previous study in the Aberdeen Birth Cohort 1921 reported an inverse association between childhood IQ and HADS-D but not HADS-A (Bain et al., 2003).

The present study contributes to the small amount of literature on childhood IQ and symptoms of anxiety and depression in older adults. Furthermore it builds on previous research by illustrating that these associations remain after adjustment for vascular risk factors, adult SES, current cognition and other early life factors. However, the lack of previous research, and the relatively small effect sizes found in this analysis, means that more studies are needed to confirm these associations.

Unlike childhood IQ, there are several studies which have examined associations between education and depression in older adults. There is much debate about whether the protective effect of education accumulates or attenuates with age. Some have argued that over the life course the protective effect of education appears to follow a curvilinear pattern with larger effects among young adults and the elderly. Other cross sectional (Miech and Shanahan, 2000, Schaan, 2014) and longitudinal (Bjelland et al., 2008) studies have shown that the difference in symptoms of anxiety and depression between high and low educational level increases with age. However other studies have found no such association (Eaton et al., 2001, Naerde et al., 2002, Bracke, 2000). Meta-analysis of 36 studies found that low education increased the risk of depression by 49-58% in people over the age of 65 (Chang-Quan et al., 2010). These findings are supported by a recent study of more than 20,000 members of the US Health Retirement Study (mean age 68) and the English Longitudinal Study of Aging (mean age 65) which found that having at least a high school education was

associated with lower symptoms of depression on the CES-D (Tampubolon and Maharani, 2017).

In contrast to depression a review of risk factors for anxiety and depression in later life identified only 3 studies (Schoevers et al., 2005, Forsell, 2000, Beekman et al., 1998) which had examined education level as a risk factor for anxiety disorder in older adults. One of these studies reported an association between education level and diagnosis of GAD (Beekman et al., 1998) but the other two reported no association. Two other previous studies have examined bivariate correlations between years of education and symptoms of anxiety. In the Aberdeen Birth Cohort 1921 there was no association between education and symptoms of anxiety on the HADS-A (Bain et al., 2003). However another study did find correlation between years of education and HADS-A score in the LBC 1921 wave 1 of the LBC 1936 (Brett et al., 2012). Findings in those below the age of 60 have found a more consistent relationship between education and anxiety (Chazelle et al., 2011, Erickson et al., 2016, Melkevik et al., 2016).

In this study associations between years of education and educational attainment and symptoms of depression and anxiety lost statistical significance after adjustment for childhood and premorbid IQ and childhood SES. Of the previous studies identified, none adjusted for childhood or premorbid IQ and only one (Melkevik et al., 2016) adjusted for childhood SES. Some have argued that education is a good proxy measure for childhood cognitive ability and therefore it is not appropriate to adjust for childhood IQ in studies of education (Deary and Johnson, 2010). However other studies have shown that controlling for intelligence in the education-health relationship has little effect and suggest that education may have a positive effect on health outcomes regardless of IQ (Link et al., 2008). More research is needed to determine whether education exerts an independent effect on anxiety and depression in later life or whether its effects are mediated by cognitive ability.

Childhood conditions have been implicated in social inequalities in adult health (Galobardes et al., 2006) and the current findings suggest that this may extend to mental health in later life. Previous findings on the relationship between childhood SES and adult mental health have used various indicators of SES including parental occupation, parental education, overcrowding and latent variables consisting of multiple measures. Non manual parental occupation has been found to be protective against depression in early adulthood (Ritsher et al., 2001, Gilman et al., 2002), mid-

life (Tiffin et al., 2005, Power et al., 2007) and later life (Luo and Waite, 2005), independent of factors such as adult SES and education, supporting the current findings in the Dutch Famine Birth Cohort. Other studies of older adults have reported independent associations between self-reported childhood SES and SES measured by material possessions in childhood (Tani et al., 2016, Tampubolon, 2015). However, some studies have reported that the association between childhood SES and mental health in mid-life and later adulthood is mediated by other factors such as education (Harper et al., 2002) (Pakpahan et al., 2017, Berndt and Fors, 2016, Schaan, 2014) and adult SES (Stansfeld et al., 2008, Colman et al., 2014, Schaan, 2014). For example, Schaan (2014) found that a high education helped overcome the negative consequence of a poor family background. Previous research in the Aberdeen Children of the 1950s cohort found that low early life social position determined by the fathers occupation level was associated with poor adult rated health but not poor mental health (Dundas et al., 2014). In line with our study they also found no association between overcrowding and either physical or mental health.

6.4.4 Possible mechanisms

There are several possible explanations for the observed associations. Exposure to an adverse prenatal environment may have long term effects on mental health through epigenetic mechanisms (Nestler, 2014) or through programming of the hypothalamic pituitary adrenal (HPA) axis (Welberg and Seckl, 2001) or stress response (Painter et al., 2006). Several studies have shown that low birth weight is associated with elevated fasting plasma cortisol concentrations (van Montfoort et al., 2005), and previous research in the Dutch Famine Birth cohort found that famine exposure was associated with increased blood pressure response to psychosocial stress (Painter et al., 2006).

Imaging studies have revealed that aspects of brain structure associated with intelligence include regions also implicated in psychiatric conditions. For example, the hippocampus is a critical brain structure involved in memory function and overall intellectual performance. Correlational studies have found that hippocampal volume is significantly positively correlated with verbal IQ in males (Schumann et al., 2007, Andreasen et al., 1993). Several studies have also found that hippocampal volume is reduced in patients with anxiety (Yamasue et al., 2008) and major depression (Koolschijn et al., 2009) with larger associations found in older adults with late life depression compared with younger patients and controls (Lloyd et al., 2004).

Additionally, the meta-analysis presented in chapter 2 found that lower childhood IQ is associated with higher white matter hyperintensity (WMH) burden in adulthood. Higher WMH burden and lower white matter integrity are also associated with depressive symptoms in older adults (van Agtmaal et al., 2017, Wen et al., 2014, Pasi et al., 2016). This suggests that lower IQ may be an indicator of neuroanatomical deficits that influence development of depression and anxiety.

Having a lower IQ or less education may make people more vulnerable to developing mental disorders because they are less able to cope with stressful life events. Several studies show that stress is common in older adults and plays a major role in the development of psychological health problems including depression (Fiske et al., 2009) and anxiety (Kogan et al., 2000). Those with lower IQ or less education may have fewer personal and social resources and therefore have less resilience to stress compared to those with a higher IQ or more education. Personal and social resources which may decrease risk of mental disorders and help buffer the effects of stress include a higher supportive social network (Pinquart and Sorensen, 2001), more coping strategies, higher self-esteem (Orth and Robins, 2013) and a higher sense of personal control (Bjørkløf et al., 2013). People with a lower IQ are also more likely to work in lower paid, lower skilled jobs which may increase exposure to psychosocial stressors in the work environment associated with psychological distress (Bonde, 2008).

Additionally, childhood IQ and education may increase mental health knowledge and mental health literacy. Health literacy is strongly associated with education (Murray et al., 2011, Clouston et al., 2017) and general intelligence (Murray et al., 2011, Serper et al., 2014) and therefore individuals with lower IQs are likely to have lower mental health literacy. Higher mental health literacy may reduce the risk and improve outcomes for psychiatric disorders by influencing when and what type of treatment is sought, promoting treatment compliance and improving symptom management and prevention (Jorm, 2012, Kelly et al., 2007). Those with higher intelligence may be more able to identify the early symptoms of mental health problems, have knowledge of help seeking options and treatments and be aware of effective self-help strategies for milder problems (Jorm, 2012).

Cognitive ability shows moderate heritability (Plomin and Deary, 2015) as do many physical and mental health illnesses (Polderman et al., 2015). Some studies have indicated that genetics could also play an important role in the aetiology of cognitive

ability and its association with health outcomes, including mental health (Hagenaars et al., 2016). For example a shared genetic aetiology has been reported between cognitive ability and autism (Hill et al., 2016, Clarke et al., 2016), schizophrenia (Kendler et al., 2015, Hill et al., 2016, McIntosh et al., 2013) and Alzheimer's disease (Hill et al., 2016) and between educational attainment and bipolar disorder (Hill et al., 2016). A recent study using linkage disequilibrium regression and polygenic profile scoring found significant genetic correlation between major depressive disorder and slower reaction time in the UK Biobank, a population sample of 12,151 individuals. Furthermore polygenic risk for major depressive disorder had a negative association with verbal-numerical reasoning (Hagenaars et al., 2016).

6.4.5 Strengths and limitations

The current research has several strengths. Firstly, this study used early life factors collected during childhood rather than retrospectively in adulthood which reduces the chances of recall bias. Collecting IQ data in childhood before any expected age-associated cognitive decline can occur reduces the chance of reverse causation. The availability of such a wide range of early life data, particularly famine exposure, is very rare and valuable. Secondly, all analyses were adjusted for vascular risk factors current cognition and adult SES and other early life factors which has not been done in other studies. Finally the total sample size was relatively large for most analyses.

Limitations of the present data include the use of self-reported measures of mental health. These measures tend to have lower validity than clinically diagnosed conditions in medical records. However the HADS has been shown to have good sensitivity for detecting symptoms of anxiety and depression in the general population (Bjelland et al., 2002). Another limitation is that there were no data on mental health at the time of the cognitive ability test (in childhood) in these cohorts. This may have been a useful covariate to include and would have determined whether concurrent mental health affected childhood IQ scores. Finally although these analyses included several covariates it was not possible to adjust for other factors which may have influenced associations such as stressful life events, parental divorce, physical illness or personality factors such as neuroticism.

6.4.6 Conclusions

The current findings demonstrate that there is a relationship between some early life factors and symptoms of depression and anxiety in older adulthood. Famine exposure

was associated with increased symptoms of depression and anxiety at 68. The results also suggest that lower childhood cognitive ability and more deprived childhood SES are associated with symptoms of depression and anxiety independent of other early life factors and common risk factors. The associations between educational attainment and psychological health were not independent of cognitive ability and childhood SES and further research is needed to confirm these findings. The current findings contribute to the understanding of how early life factors contribute to mental health in later life and can be used to help inform mental health policy and well as mental health interventions to target those most at risk. This is especially important given the high personal and societal costs and the under recognition of symptoms of anxiety and depression in the general older population.

7. Discussion

7.1 Summary of findings

This thesis examined early life influences on cerebrovascular disease and symptoms of depression and anxiety. The first aim of this thesis was to systematically review and meta-analyse all published literature on childhood cognitive ability, education and childhood socioeconomic status (SES) and risk of: (a) cerebral vascular lesions on imaging including small vessel disease (cSVD) (b) stroke and (c) post-stroke depression. The remaining aims were to examine in 4 cohorts (1) the relationship between cerebrovascular disease on MRI and self-reported symptoms of depression and anxiety (2) associations between birth and childhood factors and cerebrovascular disease on MRI and (3) associations between birth and childhood factors and self-reported symptoms of depression and anxiety. (Detailed discussion of each of these aims are presented in the relevant chapters).

This general discussion will start by giving an overview of the main findings in Chapters 2, 4, 5 and 6 and how these findings fit with the current literature. It will then discuss possible mechanisms for the findings, methodological limitations of the studies and finally some discussion of clinical implications and suggestions for future research.

7.1.2 Systematic review and meta-analysis of the current literature

The systematic review presented in Chapter 2 identified 30 relevant studies (n= 22,890) examining early life risk factors and cSVD on neuroimaging and pathology. Lower childhood IQ (5 studies) and lower childhood SES (1 study) were associated with higher WMH burden (IQ: n=1,512, r= -0.07, p=0.007; SES n= 243, deep WMH r= -0.18, periventricular WMH r= -0.15). Fewer years of education (30 studies) were associated with several CVD markers including WMH, microbleeds, lacunes and infarcts (n= 15,439, OR= 1.17, p=0.003).

90 studies were identified examining early life factors and clinically evident stroke. Stroke risk increased with lower childhood IQ (9 studies, n=1,209,952 HR= 1.17, p=0.04), lower education (79 studies, n=2,881,067, OR= 1.35, p<0.001) and lower childhood SES (10 studies, n=1,354,899, OR= 1.28, p<0.001).

33 studies (n= 8438) were identified examining education level and post-stroke depression. One study examined premorbid IQ in those with and without post-stroke depression. Although IQ was higher in those without depression this difference was not statistically significant. No studies examined childhood SES and post-stroke depression. Low education was associated with increased risk of post-stroke depression (OR= 1.16, p=0.01) and those with post stroke depression had fewer years of education than those without post-stroke depression (MD= 0.68, p=0.04).

The main limitation of this systemic review was that most of the identified studies did not adjust for risk factors such as smoking or hypertension in adulthood, for adult SES or for the effect of other early life factors on each other. Many of the effect sizes were calculated using frequency data which meant they were crude. Furthermore there was evidence of publication bias in many of the analyses. Therefore it was concluded that more studies were needed to assess associations between early life factors and cSVD after adjustment for known risk factors and other early life factors.

7.1.3 Cerebrovascular disease and symptoms of anxiety and depression

Chapter 4 examined concurrent associations between markers of cSVD, whole and regional brain volumes and self-reported history of stroke and self-reported symptoms of anxiety and depression. The findings provide some evidence for the association between structural brain changes and depressive symptoms, but not symptoms of anxiety in later life.

Depression and anxiety are two of the most common neuropsychiatric disturbances following stroke with a prevalence of 31% (Hackett and Pickles, 2013) and 20-25% (Campbell Burton et al., 2013) respectively. In Chapter 4 history of stroke and imaging evidence of infarcts in the LBC 1936 were associated with higher depressive symptoms. However there was no association with symptoms of anxiety. There was also no association between anxiety and markers of cSVD or brain volumes. Unlike depression, neuroimaging data on anxiety in older adults is limited and has primarily focused on grey matter structures. Studies in younger adults have reported an inverse correlation between parahippocampal-amygdala regions volume and self-reported symptoms of anxiety (Spampinato et al., 2009) and increased activity in the amygdala (Meaney et al., 2015). The data presented in Chapter 4 is the first to examine multiple markers of cSVD and total cSVD burden and symptoms of anxiety in parallel with depression in the same individual. Previous studies including in the LBC 1936 found

no association between white matter integrity and symptoms of anxiety in healthy adults (Bijanki et al., 2013, McIntosh et al., 2012). However one study did find an inverse association between white matter integrity and anxiety in patients with atherosclerotic vascular disease suggesting that there may be specific relationships of white matter health and anxiety symptoms in patients with more severe vascular disease (Bijanki et al., 2013). Alternatively anxiety may have been spurious or may be more associated with grey-matter structures or markers of brain function rather than structure (McIntosh et al., 2012).

The vascular depression hypothesis, previously described in section 1.2 proposes that cSVD leads to depressive symptoms by disruption of deep and frontal brain structures or their connecting pathways involved in mood regulation (Alexopoulos et al., 1997a, Krishnan et al., 1997). Previous research in the vascular depression hypothesis has focused mainly on the role of WMHs and has reported associations between WMH burden and white matter integrity and depressive symptoms (McIntosh et al., 2012). Findings on cSVD markers other than WMH and depressive symptoms have been mixed (van Sloten et al., 2015, Direk et al, 2016, Pasi et al., 2016). Data presented in Chapter 4 are the first to examine total cSVD burden and depressive symptoms. There was no association between individual cSVD markers or total cSVD burden and depressive symptoms in individual cohorts or in the meta-analysis of all cohorts. However the point estimates were in the expected direction and the studies may have been underpowered. Lower visually rated atrophy, higher whole brain volume as percentage of the ICV (a marker of global atrophy), higher whole brain volume corrected for ICV and higher global grey and white matter volumes were associated with lower depressive symptoms Depression scores in all cohorts were low (median of 2-3) and it is possible that associations between cSVD and depressive symptoms may be stronger in samples with higher depressive symptoms or more cSVD. For example a previous study by Direk and colleagues (2016) found no association between microbleeds and depressive symptoms but did find that microbleeds increased the risk of diagnosis of a major depressive disorder (MDD) (Direk et al., 2016). Similar findings have been reported for EPVS and depression (Patankar et al., 2007, van Sloten et al., 2015). Furthermore, data from Chapter 4 found that in the Simpson cohort, which is the oldest cohort with the highest cSVD burden and higher depression scores, WMH volume was associated with depressive symptoms which supports previous findings.

Identification of structural imaging markers associated with psychiatric symptoms in older adulthood could provide useful biomarkers for predicting risk of depression and treatment response. Several studies have reported associations between WMH burden and treatment response in later life depression (Sheline et al., 2010). However this is not supported by all studies or by some of the analyses in this chapter.

7.1.4 Early life factors and cerebrovascular disease

Chapter 5 examined associations between early life factors and total and individual markers of cSVD and total and regional brain volumes after adjustment for vascular risk factors and adult SES. Early life factors included birth factors (prenatal malnutrition (Dutch Famine Birth cohort only), birth weight, birth length and ponderal index) and childhood factors (childhood cognitive ability, education and measurements of childhood SES).

Birth weight and placental weight were the only birth factors which showed statistically significant associations with structural brain changes. Increasing birth weight was associated with fewer lacunes (Dutch Famine Birth Cohort, the LBC 1936 and the Simpson cohort) and increased ICV (LBC 1936 and Simpson cohort). Low birth weight is considered to result from slow intrauterine growth. According to the Developmental Origins of Health and Disease (DOHAD) hypothesis, previously described in Chapter 1, undernourishment during gestation (indicated by low birth weight) can lead to metabolic adaptions which can persist to adult life and predispose to illness (Barker, 2003) . Several studies have shown that low birth weight is associated with increased risk of stroke and coronary heart disease (Rich-Edwards et al., 2005) and previous research in the Simpson cohort found that birth weight was associated with frontal white matter integrity (Shenkin et al., 2009). The data presented in this thesis are some of the few to examine birth weight in relation to cSVD or brain atrophy in older age.

Increasing placental weight was associated with lower total cSVD burden, WMH burden and WMH volume and fewer infarcts. Associations between placental weight and WMH burden and WMH integrity were also reported by Shenkin et al (2009). The current thesis suggests that placental weight may be associated with other markers of CVD in addition to WMH. However these effects were small and data were only available for the Simpson cohort which has a small sample size and so must be interpreted with caution. Ideally this finding should be investigated in larger cohorts.

However placental weight is not routinely collected in the UK anymore and so future UK studies would have to use data linkage between birth records which included placental weight and health records or be designed to collect placental weight prospectively.

The analysis of childhood factors and cSVD in Chapter 5 built on the systematic review presented in Chapter 2 by adjusting associations between childhood IQ, education and childhood SES and cSVD for age, sex, hypertension, smoking, adult SES and each early life factor. This is important given the complex relationships between vascular risk factors and cSVD. Increasing childhood IQ was associated with lower total cSVD and WMH burden, fewer lacunes and fewer infarcts. More education was associated with fewer microbleeds and fewer infarcts. Increasing premorbid IQ was associated with decreased global brain atrophy and increased total brain volume corrected for ICV. Increasing childhood and premorbid IQ and increasing years of education were also associated with higher ICV, a measure of maximal brain size. Fewer associations were found between measures of childhood SES and cSVD or brain volumes. The association between childhood IQ and WMH burden lost statistical significance after further adjustments were made for education level and childhood SES suggesting that multiple early life factors may contribute to WMH burden in later life.

The effect sizes of some analyses were small and not all early life factors were associated with cSVD. However overall these findings are consistent with the suggestion that factors other than traditional vascular risk factors may contribute to cSVD pathology and structural brain changes in later life.

7.1.5 Early life factors and symptoms of anxiety and depression

Chapter 6 examined associations between early life factors and self-reported symptoms of depression and anxiety on the HADS and QIDS-16. The first main finding was that in the Dutch Famine Birth Cohort exposure to famine, both before conception and during early gestation, was associated with increased symptoms of depression and anxiety at age 68. This was independent of education level and childhood SES (IQ not available). This suggests that the DOHD hypothesis may extend to mental as well as physical health. In contrast, there was no association between birth size measures and symptoms of depression and anxiety in any of the cohorts. In epidemiological studies birth size is a convenient measure to collect and

often provides the most accurate available indicator for estimating the effects of a suboptimal intrauterine environment. However measures such as birth weight and length are crude indictors of the intrauterine environment. For example, in the Dutch Famine Birth Cohort famine exposure has been found to have little effect on birth weight (Ravelli et al., 1998) and the prenatal glucocorticoid programming of blood pressure has been reported without affecting birth weight (Huh et al., 2008). Therefore, birth weight may underestimate the effects of a suboptimal prenatal environment and may have underestimated the effects of such an environment on mental health in the cohorts in this Thesis.

The second main finding was that childhood and premorbid IQ and having qualifications (vs no qualifications) were associated with lower symptoms of anxiety. More education was also associated with lower depressive symptoms and low childhood SES with more depressive symptoms. The association between childhood IQ and anxiety was independent of education and childhood SES. Associations between education and anxiety and depression lost statistical significance after adjustment for childhood IQ. This suggests that associations between education and symptoms of anxiety and depression may be mediated by other early life factors. Mediation of associations between education and health outcomes by childhood IQ has been discussed in general (Gottfredson, 2004) but no studies have examined this in relation to anxiety and depression in later life and so this should be explored in future research.

7.2 Mechanisms

There are several mechanisms which may explain the findings presented in this Thesis. Early life exposures may induce changes in the epigenome, may lead to better brain integrity or resilience or may influence later health behaviours and lifestyle factors. These will be explored in the following section.

7.2.1 Epigenetic mechanisms during gestation

Developmental programming, described in detail in Chapter 1, is thought to be the process by which early life exposure to environmental adversities during critical periods of development affect the structure and physiology of cells and organs resulting in long term changes in tissue function (Barker, 2003). Changes occurring in utero may provide immediate benefits to foetal survival but they can predispose to disease in later life. At the molecular level there is evidence to suggest that these

changes in physiology are mediated in part by alterations in gene expression (Saffery and Novakovic, 2014). These modifications are referred to as epigenetic as they involve changes to the gene expression without changes to the DNA sequence. The best characterised epigenetic modification is cytosine methylation which occurs by the addition of a methyl group to DNA most frequently within cytosine phosphate guanine (CpG) dinucleuotides. The addition of these marks to DNA or proteins (histones) around which the DNA is wrapped often modifies the function of the gene and is used to supress or silence gene expression. When the wrong type of epigenetic marks are introduced this can result in disease or increased risk of disease. For example, cancer is often associated with hypomethylated DNA and notable hypermethylation of tumour suppressor genes compared to normal tissue (Phillips, 2008).

Many epigenetic changes occur in early development and their effects can persist into adulthood, therefore epigenetic modifications are widely hypothesised to be an overarching mechanism linking maternal nutrition to health phenotypes in the offspring (Duncan et al., 2014, Gluckman and Hanson, 2008). Epigenetic marks undergo critical modifications during early development. This is when the plasticity of each tissue or organ is at its highest and when the epigenetic system is most sensitive to environmental exposures. The most sensitive window for epigenetic effects is different for each tissue however once a tissue is fully developed it is less sensitive to alterations by environmental stimuli (Heindel and Vandenberg, 2015).

Brain development begins approximately 22 days after conception when the neural plate begins to fold inwards forming the neural tube which eventually becomes the brain and spinal cord (Mundy and Vilchez, 2018). The brain continues to mature and develop well into adolescence, retaining a baseline level of plasticity making it particularly susceptible to environmental adversities and epigenetic change both during gestation and early life (Bale, 2015). For example a longitudinal epigenetic study found that the association between lower SES in adolescence and threat related reactivity of the amygdala (involved in various autonomic responses to stress including activation of the HPA axis) was mediated by methylation of the proximal promoter region of the serotonin transporter gene (Swartz et al., 2017).

Healthy brain development and DNA methylation are dependent on several enzymes in the presence of dietary micronutrients, particularly methyl-donors such as folate, choline and betaine. Evidence from animal models and some evidence from human

studies shows that supplementation or restriction of the maternal diet can have permanent effects on gene expression by changing epigenetic marking in the offspring. In particular animal studies on dietary choline provide good examples of nutrient responsive epigenetic mechanisms and brain development. In rodents decreased supply of choline during critical periods of brain development (days 11-17 of gestation), results in diminished methylation of genes involved in brain development (Mehedint et al., 2010, Wang et al., 2016). This resulted in small foetal brains, decreased neurogenesis in the cortex (Wang et al., 2016) and hippocampus (Craciunescu et al., 2003, Albright et al., 1999, Jadavji et al., 2015), changes in hippocampal function such as altered long term potentiation (Jones et al., 1999, Montoya et al., 2000, Pyapali et al., 1998), and worse visuospatial and auditory memory (Meck and Williams, 1999, Meck et al., 1988). Conversely supplementation of choline during this critical window is associated with enhanced long term potentiation as adults (Pyapali et al., 1998, Montoya et al., 2000, Jones et al., 1999) and improved visuospatial and auditory memory which lasts for their lifetime (Meck et al., 2007, Meck et al., 1988, Meck and Williams, 2003). Furthermore choline supplementation has been shown to prevent the age related memory decline often seen in rats (Meck et al., 2007). Studies in humans have found that babies born to women who consume higher levels of choline during pregnancy perform better on tests on information processing speed (Caudill et al., 2017) and visuospatial memory (Boeke et al., 2012), suggesting that the effects of choline on brain development may also apply to humans.

Studies on prenatal nutrition and epigenetic mechanisms in humans remain limited. In the Dutch Famine Birth cohort there are persistent differences in whole blood DNA methylation in adults who were exposed to famine in early gestation compared to unexposed individuals (Heijmans et al., 2008, Tobi et al., 2009, Tobi et al., 2014, Tobi et al., 2012). Furthermore a previous genome wide DNA methylation analysis study compared members of the Dutch Famine Birth cohort at age ~59 years and sibling matched controls. There were associations between famine exposure in early gestation but not mid or late gestation and DNA methylation at specific CpG dinucleotides linked to genes involved in growth, cellular differentiation and metabolism (Tobi et al., 2015). Collectively these findings suggest that early gestation may be a uniquely sensitive period for establishing and maintaining epigenetic marks.

Epigenetic dysfunction in the brain is associated with several neuropsychiatric disorders (Nestler, 2014) and DNA methylation plays an important role in the susceptibility to depression (Mill and Petronis, 2007, Schroeder et al., 2010) and anxiety (Bartlett et al., 2017). For example increased DNA methylation of the proximal promoter region of the serotonin transporter gene has been associated with higher depressive symptoms (Zhao et al., 2013) and increased threat related amygdala reactivity (Nikolova et al., 2014, Swartz et al., 2015), the latter of which is consistently observed in patients with depression and anxiety (Etkin and Wager, 2007, Groenewold et al., 2013).

Endocrine hormones including insulin, insulin-like growth factors (IGFs), thyroid hormones and glucocorticoids regulate foetal growth and development and therefore have an important role in foetal programming (Welberg and Seckl, 2001). Furthermore glucocorticoids, particularly cortisol, regulate the biological stress response. The foetal hypothalamic-pituitary-adrenal (HPA) axis is sensitive to the intrauterine environment and exposure to undernutrition may alter the set point of the HPA axis leading to increased concentration of cortisol (Welberg and Seckl, 2001). In animal models exposure to undernutrition during gestation is associated with increased post-natal HPA activity (Bloomfield et al., 2003, Lesage et al., 2001). In humans, low birth weight is associated with elevated fasting plasma cortisol concentrations (van Montfoort et al., 2005). However studies in the Dutch Famine Birth cohort found no differences in cortisol concentrations following the dexamethasone suppression test or cortisol production in response to psychosocial stress between famine exposed and unexposed cohort members (De Rooij et al., 2006a, de Rooij et al., 2006c). On the other hand blood pressure response to psychosocial stress tests are higher in those exposed to famine in early gestation (Painter et al., 2006). This suggests that stress appraisal may be higher in those prenatally exposed to famine but famine exposure does not affect HPA activity. Furthermore, blood pressure responses to psychosocial stress have been associated with methylation patterns of the glucocorticoid receptor, suggesting a possible role of epigenetic processes (de Rooij et al., 2012).

7.2.2 Brain integrity and resilience

The theory of brain reserve suggests that early exposure to cognitively stimulating experiences may provide benefits in brains structure and function and may be protective against age related changes or brain pathology (Stern, 2002, Stern, 2006).

Experience-dependent plasticity refers to the way the brain organises itself in response to an individual's experience and acquired skills. This has been found across many neural systems during childhood and continues throughout the lifespan. Experience-dependent plasticity leads to synaptic pruning whereby repeated use strengthens synapses while infrequent use leads to synaptic elimination. Studies in rodents have found that exposure to enriched environments can induce numerous changes in the brain both at the cellular and molecular level including increased neurogenesis, angiogenesis and synaptogenesis (Gelfo et al., 2018). These changes are mainly seen in areas of the brain that have the ability to undergo substantial synaptic plasticity such as the hippocampus and neocortex (Gelfo et al., 2018).

Education and early life IQ may be a marker of brain resilience to age related pathology such as cSVD, as seen by the associations between IQ and cSVD presented in Chapter 5. Previous research has found that the cortex is thicker in 70 year olds who scored higher on IQ tests at age 11 which may protect against accumulating cSVD (Karama et al., 2014). Furthermore hippocampal volume, which is reduced in older patients with anxiety and major depression, has been found to be positively associated with IQ (Schumann et al., 2007, Yamasue et al., 2008, Koolschijn et al., 2009). Alternatively, education and IQ may increase the threshold of pathological load required before disease is clinically evident. High levels of education or cognitive ability may be indicative of a larger brain or synapse count (brain reserve) or more efficient brain networks that are less susceptible to disruption (cognitive reserve). Cognitive reserve may also involve the use of brain networks that are not usually used in order to compensate for brain damage (Stern, 2002). This theory has largely be used to explain individual differences in cognitive impairment and dementia. Whether it is applicable to symptoms of anxiety and depression in older adults has not yet been be tested and is a target for future research.

There is a broad consensus that intelligence is linked to characteristics in the neural system. Imaging studies in children have shown that the integrity of connections between multiple brain areas are associated with numerical abilities and more efficient and advanced problem solving techniques in school aged children (Evans et al., 2015, Qin et al., 2014). Furthermore more years of education are associated with more specialised use of neural processing and more efficient brain networks (Marques et al., 2016). Education is the main predictor of fibre tract integrity in several brain areas with those with higher levels of education having more richly connected fibre tracts

(Teipel et al., 2009). It has been suggested that the association between brain structure and intelligence may partly be explained by information processing speed. Efficient information processing speed which correlates with intelligence (Deary et al., 2006, Yu et al., 2008, Chiang et al., 2009), is thought to rely on the integrity of white matter tracts connecting distal brain areas (Deary and Johnson, 2010, Jung and Haier, 2007, Neubauer and Fink, 2009). Studies using DTI showed significant correlations between white matter integrity and intelligence in children (Schmithorst et al., 2005) and young adults (Chiang et al., 2009). Furthermore longitudinal studies have reported that white matter integrity at age 83 correlates with age 11 IQ (Deary et al., 2006).

The extent to which brain integrity protects against CVD and mental health in later life and whether such associations can be influenced by exposure to more or less education, is not clear.

7.2.3 Behaviour and lifestyle

Education can shape access to social and economic resources including better health care and better job opportunities. Individuals with low education are more likely to work in lower skilled jobs and may be exposed to more hazardous and stressful working conditions. They may have fewer personal resources to help buffer the effects of stress such as a lower supportive social network, fewer coping strategies and lower self-esteem. Intelligence may influence adoption of certain behaviours that are beneficial to health such as level of exercise, diet and alcohol consumption and self-management of vascular risk factors which influence risk of CVD. Furthermore education and Intelligence are associated with better health literacy which can reduce the risk and improve outcomes of both physical and mental health conditions. Those with higher health literacy may be more likely to identify early symptoms of illness and seek help, may be better at managing symptoms and more likely to comply with treatment.

7.3 Methodological considerations

Specific limitations have been discussed in each of the previous chapters. This section will therefore focus on general methodological limitations of the current Thesis.

This thesis used participants from 4 historical cohort studies who were all traced in middle-old age using either childhood survey records (STRADL and LBC 1936) or birth records (Dutch Famine Birth cohort and Simpson cohort). This may have led to bias in the samples as loss to follow up rarely occurs at random and has been associated with sociodemographic factors and health outcomes (Launer et al., 1994). In STRADL response rates were associated with higher childhood cognitive ability and higher childhood SES and in the Dutch Famine Birth cohort women exposed to famine in early gestation had higher overall mortality up to the age of 63 (before recruitment to the current study began) compared to those who weren't exposed (van Abeelen et al., 2012). The data were not available to compare participants and refusers in each of the four studies and so it is not possible to determine the extent of the bias in these samples.

It is also possible that participants are not representative of the general older population in Edinburgh, Aberdeen or Amsterdam. Exclusion criteria in all studies was kept to a minimum to allow as many people as possible to participate, however self-selecting samples are often high-functioning and well-educated. The mean MHT score for the LBC 1936 at age 11 was 49.0 (11.8) compared with 34.5 (15.5) for the whole of Scotland and 40.3 for the whole Edinburgh region. In the Simpson cohort premorbid IQ was also slightly higher than the general population (NART score of 106). In terms of vascular risk factors there were fewer current smokers in the samples as a whole compared to the national average. However the rates of diabetes were the same as the UK average and the prevalence of hypertension was higher than that reported in the UK (Pierce et al., 2009, Government Statistical Service, 2016).

Another possible limitation is that structural brain changes and symptoms of anxiety and depression were measured at one time point only. It is possible that some of the significant associations may be due to factors accrued at any point in the lives of the participants and not necessarily as a result of ageing. Meta-analysis has found that older depressed patients with early onset of their illness have more severe WMH burden compared to late onset, despite the longer duration of illness (Herrmann et al., 2008). It was not possible to examine lifetime history of mental health problems in this Thesis and therefore it is not clear whether the symptoms of depression and anxiety in these participants began in later life or in earlier adulthood.

This thesis examined a large number of associations and did not correct for multiple testing. It is therefore possible that some of the significant findings, particularly those

of borderline statistical significance, could be due to chance. It has been argued that correction for multiple testing increases the possibility for false negative findings (type II error) and should be used with caution in studies with hypothesis-driven analyses (Rothman, 1990). However these findings should still be replicated, particularly those that have not been examined before.

All cohorts used in this thesis are from Northern Western Europe which limit the generalisability of the findings to parts of the world. However the meta-analysis presented in Chapter 2 found there was no difference in associations between education and stroke or post-stroke depression in studies conducted in Western Europe and North America and those conducted in the Asia Pacific region.

Finally, it is possible that associations may be affected by a third confounding variable or set of variables. These may be other early life factors, vascular risk factors or factors not captured in the current data. This Thesis built on previous research by including several covariates in all analyses however some have suggested that these factors should be treated as confounders or mediators instead of only covariates. An example of this in the literature is the association between cSVD and cognition. Among those with low levels of education the presence of WMH or lacunar infarcts is associated with lower cognition (Farfel et al., 2013, Dufouil et al., 2003). However, for those with more years of education the likelihood of cognitive impairment from WMH and lacunar infarcts is much lower (Farfel et al., 2013, Dufouil et al., 2003). Education may be a confounder as it may affect the exposure (education) and outcome (WMH) without changing the size or direction of the effect or it may be a mediator and be on the causal pathway between the two. This could be evident in the current data. For example in some analyses childhood IQ was associated with WMH burden and symptoms of depression. Mediation analysis such as structural equation modelling could be used to test whether WMH burden is the casual pathway through which childhood IQ is associated with depressive symptoms. This wasn't done in the current thesis due to time constraints but is a target for future research.

It should be noted that the effect sizes for some analyses were relatively small and many were neutral or not statistically significant. For example an increase of one childhood IQ point was associated with a 1% lower risk of moderate to severe WMH burden. This may seem like a very small effect at the individual level but even such small influences can have important effects at a population level (World Health

Organization, 2002). Nevertheless these associations should be interpreted with caution.

There were also strengths. The main strength was the availability of the large amount of early life data and later life neuropsychiatric and imaging data which is not always available. There were a large number of MRI examinations performed. Both structural and qualitative imaging methods were employed to a high standard using validated methods. Finally all analyses were adjusted for a wide range of confounders which had not been done in previous research.

7.4 Implications of findings and future directions

The findings of this thesis potentially have important implications for public health. However many of the effect sizes are small or neutral and some are of borderline statistical significance and therefore the true impact of these findings are unclear.
As discussed in Chapter 1 cerebrovascular disease, depression and anxiety are serious health conditions which are common in the general older adult population. They have substantial cost implications for the national economy and cause a significant amount of distress disability to patients and carers. Stroke and cSVD increases the risk of and are a major cause of cognitive impairment and dementia. Furthermore cognitive impairment, depression and anxiety increase the risk of stroke (Lambiase et al., 2014, Dong et al., 2012). Dementia and stroke are major government and NGO targets with UK dementia policy (2009, Parkin and Baker, 2016) focusing on early screening, assessment and diagnosis to enhance patient quality of life and improve care. However a better understanding of the lifetime risk factors is important to inform prevention and these results indicate effective prevention could be better served by policy changes which address issues as early as prenatal care.

Clinicians and policy makers rarely relate disease in later life to events in childhood instead focusing on management of mid to late life risk factors. The cause of cSVD is largely unknown and as a result prevention and treatment options, which mainly include management of traditional risk factors, are largely suboptimal. For example antihypertensive treatment reduced WMH progression in some observational studies (Dufouil et al., 2001) but showed little or no effect in randomised control trials (Dufouil et al., 2005, Weber et al., 2012). Similarly antidepressant medication, which is used to treat major depressive disorder (MDD) and generalised anxiety disorder (GAD) are only partially effective. Furthermore patients may not receive medication for

symptoms of depression and anxiety that do not meet the full diagnosis criteria for MDD or GAD despite their high prevalence and resulting impairment. In individual patients, awareness of early life influences would increase knowledge of elevated risk above that suggested by midlife factors alone which might improve patient management.

Few previous studies have investigated multiple early life factors and CVD and symptoms of depression and anxiety in later life. More research should be conducted to examine whether associations with early life factors differ in those with more vascular disease or more symptoms of depression and anxiety. Future studies of clinical and population cohorts should examine the interrelationships between early life factors and underlying mechanisms which could determine whether the risk factors in early life are modifiable. This may help inform future interventions and planning of health and educational services to target those most at risk. However interventions to affect early life education are complex and may require changes to social policy or public health strategy which may be difficult due to the long time lag between exposure (as early as infancy) and health outcomes in later life.

Does education or childhood IQ directly cause differences in cSVD or symptoms of anxiety and depression? There are several factors which can be considered when determining whether an association is likely to be causal. These include biological plausibility, temporality, consistency, strength of association and experiment (Bradford-Hill 1965). The data presented in this Thesis satisfies some, but not all, of these criteria. For example associations between early life factors and cerebrovascular disease and depression and anxiety are biologically plausible and are supported by the DOHD hypothesis and the theory of brain reserve. This study also had measures of IQ, education and SES obtained in childhood before cSVD would have been evident. This reduces the chance of reverse causation and supports the temporality assumption of causality. The current findings are also supported by previous research which has been outlined in the previous chapters and the meta-analysis presented in Chapter 2. However having a measure of IQ in childhood is rare and as a result much of the previous research on childhood IQ and later health has been conducted in Scottish birth cohorts. Further investigation of associations between childhood IQ and later health in larger more diverse populations may help further determine the causal effect of IQ on later health. Furthermore measures of education based on years or qualifications do not capture the quality of education

received or variation in school term duration. These factors may be differentially associated with health outcomes which would violate the consistency assumption of causation.

The effect sizes reported in this Thesis are small. In general the stronger an association between cause and effect the less likely it is that the relationship can be explained by other factors. However with health outcomes, which are multifactorial, not all causes will have strong effects if they are necessary but not sufficient to cause the outcome alone. For example one study examining the impact of fruit consumption on cancer report a hazard ratio of ~0.999 per serving (Boffetta et al 2010). Conversely very large effects may be due to error, bias or small sample size.

The strongest support for causation comes from experimental or semi experimental studies. Much of the evidence about the effects of early life factors on health, including the data presented in this Thesis, comes from observational studies which can be affected by residual confounding, even after adjustment for other risk factors. Whilst randomised control trials are unlikely to be ethical or cost effective, previous studies have exploited natural experiments such as the increase in the minimum school leaving age which affected people from all backgrounds. One study (Davies et al 2018) examined over half a million participants from UK Biobank who were attending school in 1972 when the school leaving age was changed from 15 to 16. Using inverse probability weighting the authors found consistent evidence that remaining in school for an extra year causally reduced the risk of diabetes and mortality in adulthood.

Increases in education are often accompanied by general social development which is also linked to better health. Two population surveys of individuals aged 65 years and older, The Cognitive Function and Ageing Studies (CFAS) I and II, reported a decline in age specific prevalence and incidence rates among people born later in the first half of the 20th century (Matthews et al 2013, Matthews et al 2016). The standardised dementia prevalence rates were 8.3% in CFAS I (conducted 1989-1994) compared to 6.5% in CFAS II (conducted 2008-2011) (Matthews et al 2013). Furthermore incidence of dementia decreased by 20% between CFAS I and CFAS II (Matthews et al 2016). The authors concluded that reductions in inequality and societal changes such as improvements in living conditions, higher levels of education and improved cognition across generations may reduce the risk of late-life dementias in people who survive to old age.

The current findings, particularly those presented is Chapter 6, have implications for maternal health. Nutrient restriction during and in the months before conception was associated with the mental health of the offspring nearly 70 years later. This finding highlights the importance of reinforcing balanced nutrition and promoting coping strategies throughout pregnancy. Whilst a situation like the Dutch Famine is unlikely to occur again prenatal nutrition is a very real concern in the growing number of families living in poverty. Foetal undernutrition may also result from maternal dieting, eating disorders, placental insufficiency and hyperemesis gravidarum. On a global level inadequate micronutrient intake is common among pregnant women living in developing countries (Darnton-Hill and Mkparu, 2015) and migrant populations who shift to a richer nutritional environment between gestation and childhood show an elevated risk of heart disease and diabetes (Barnett et al., 2006, Misra et al., 2005, Stanhope and Prior, 1980).

Current evidence of foetal influences on later health has been mainly linked to maternal undernutrition but there is now increasing epidemiological evidence that foetal over nutrition can produce similar phenotypes in the offspring. This is especially important for many developed countries where obesogenic environments and overconsumption is an increasing problem. An estimated 600 million adults worldwide are currently obese and approximately 50% of pregnant women from developed countries are either overweight or obese (Grivell et al., 2016). Obesity before or during pregnancy can lead to high glucose levels and is a major risk factor for gestational diabetes mellitus (GDM). Foetal exposure to GDM may affect development of organs involved in cardiovascular health and potentially influence later development of chronic diseases (Symonds et al., 2013, Symonds et al., 2009). Maternal obesity is associated with increased mortality (Reynolds et al., 2013), stroke and coronary heart disease (Eriksson et al., 2014) in adult offspring and increased affective disorders in children (Robinson et al., 2013). Whether or not prenatal caloric excess is associated with cSVD or mental health in older adults has not yet been investigated and is a target for future research.

Future studies should further explore the genetic and epigenetic mechanisms involved in developmental programming. Many studies have shown associations between adult disease as a result of maternal nutrition and epigenetic changes. However the mechanisms underlying these associations are not fully understood. For example whether DNA methylation truly mediates the impact of maternal nutrition on

later health or is only an indicator of exposure is still not clear and must be explored further. A better understanding of the mechanisms by which maternal diet affects health outcomes could lead to improved maternal dietary recommendations and facilitate better disease prevention strategies and therapies for the offspring. Since epigenetic effects are potentially reversible, once the mechanisms behind epigenetic changes are understood, better therapeutic interventions and strategies aimed at removing inappropriate epigenetic marks can be devised and implemented. Although epigenetic pharmacological therapies do exist they have been criticised for being unspecific (Hamm and Costa, 2015).

Large longitudinal life-course observational studies beginning before birth will help to further explore associations between early life factors and later health. Detailed information from childhood to adulthood including multiple measures of mental and physical health, vascular risk factors, genetics and brain imaging will help distinguish prenatal influences from influences occurring in childhood and throughout the life course. Combining brain imaging with genetic data, biomarkers and environmental risk factors could determine the reasons for associations between early life factors, CVD and mental health. This will also help indicate which measures are better predictors of later health and identify proximal and distal influences on development. Additionally it will allow researchers to trace the impact of life events and to record aging trajectories. The recent increase in the number of large longitudinal birth cohorts with detailed collection of environmental and other data and multiple biospecimens will greatly facilitate advances in this field but will take decades to complete.

7.5 Final conclusions

This Thesis has examined associations between early life factors, both from birth and during childhood and cerebrovascular disease and symptoms of depression and anxiety in four longitudinal cohort studies of people aged 68-82 years. Overall results suggest that early life factors, particularly childhood IQ, may contribute to structural brain changes and symptoms of anxiety and depression in later life. However many of the effect sizes are small and some are of borderline statistical significance. Therefore more research is needed to robustly test these associations in those with more vascular disease and more depression.

8. Appendices

Appendix 2.A: Search Strategy for the systematic review

MEDLINE Search Strategy

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or carotid stenosis/ or cerebral small vessel diseases/ or cerebral amyloid angiopathy, familial/ or stroke, lacunar/ or intracranial arterial diseases/ or cerebral arterial diseases/ or intracranial arteriosclerosis/ or exp "intracranial embolism and thrombosis"/ or exp stroke/ or leukoencephalopathies/ or leukoaraiosis/
2. exp *brain/ and *atrophy/
3. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva)).tw.
4. ((brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebral artery or MCA$ or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) adj6 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$)).tw.
5. ((cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or MCA$ or anterior circulation or posterior circulation or basilar artery or vertebral artery or space-occupying) adj6 stroke$).tw.
6. ((brain or cereb$) adj6 (vascular or microvascular) adj6 (disease$ or disorder$)).tw.
7. (intracranial adj6 (disease$ or disorder$)).tw.
8. (cerebral adj6 (small vessel disease$ or microangiopath$ or amyloid angiopath$)).tw.
9. ((lacun$ or subcortical) adj6 (stroke$ or infarct$)).tw.
10. (leukoencephalopath$ or leukoaraiosis).tw.
11. (white matter adj6 (disease$ or hyperintensit$ or intensity$ or change$ or lesion$ or damage or abnormalit$ or integrity or tracts or infarct$ or structure)).tw.
12. ((brain or cerebral or intracranial) adj6 (arteriosclero$ or atherosclero$ or atrophy$ or microbleed$ or microhaem$ or microhem$)).tw.
13. exp *intracranial hemorrhages/ and (microbleed$ or microhaem$ or microhem$).tw.
14. or/1-13

15. cognition disorders/ or mild cognitive impairment/ or dementia/ or dementia, vascular/ or dementia, multi-infarct/
16. neurobehavioral manifestations/ or confusion/ or memory disorders/
17. mental processes/ or cognition/ or cognitive reserve/ or Arousal/ or Orientation/ or Attention/ or exp memory/ or perception/ or exp thinking/ or Awareness/ or Problem Solving/

or "Generalization (Psychology)"/ or "Transfer (Psychology)"/ or comprehension/ or Impulsive Behavior/ or Learning/
18. ((cogniti$ or arous$ or orientat$ or attention$ or concentrat$ or memor$ or recall or percept$ or think$ or sequenc$ or judg?ment$ or awareness or problem solving or generali?ation or transfer or comprehension or learning or mental process$ or (concept adj5 formation) or executive function$) adj6 (ability$ or function$ or difficult$ or impair$ or process$ or skill$ or performance or reserve or disorder$ or manifestation$ or declin$ or dysfunct$ or deficit$ or disabilit$ or problem$)).tw.
19. (cognition or confusion or dysexecutive syndrome$ or impulsive behavio?r$ or executive dysfunction$).tw.
20. or/15-19

21. exp intelligence/ or exp intelligence tests/
22. aptitude/ or aptitude tests/ or language tests/
23. education/ or educational status/ or exp educational measurement/
24. (intelligence or intelligent or IQ or intellectual or aptitude).tw.
25. (language adj6 (test$ or ability)).tw.
26. (education$ adj6 (status or attainment or measurement$)).tw.
27. ((mental or intellect$) adj6 (capacit$ or capabilit$ or abilit$ or performance)).tw.
28. or/21-27
29. child/ or child, preschool/ or adolescent/ or adult children/
30. (child$ or adolescen$ or youth or early life or early adult or pre-adult or early year$ or premorbid or pre-morbid).tw.
31. 29 or 30
32. 28 and 31

33. Education/ or Socioeconomic factors/ or educational status/ or educational measurement/ or psychology, educational/ or achievement/
34. (education or school$ or preschool or college or university or literate or literacy).tw.
35. ((educat$ or academi$ or schola$) adj6 (achieve$ or attain$ or level or qualification$ or performance or status)).tw.
36. or/33-35

37. socioeconomic factors/ or exp poverty/ or social class/ or social mobility/ or employment/ or unemployment/ or exp family characteristics/ or exp income/ or exp occupations/
38. ((soci$ or economic or living or family) adj6 (condition$ or factor$ or status or inequalit$ or standard$ or characteristic$ or size$ or wealth or position or depriv$ or income)).tw.
39. 37 or 38

40. child/ or child, preschool/ or adolescent/ or adult children/ or fathers/ or mothers/ or parents/
41. (child$ or adolescen$ or youth or early life or early adult or pre-adult or early year$).tw
42. 40 or 41
43. 39 and 42
44. ((father$ or mother$ or parent$) adj6 (income$ or occupation$ or job$)).tw
45. 43 or 44

46. 14 and 20 and 32 (CVD, cog and IQ))
47. 14 and 20 and 36 (CVD, cog and education)
48. 14 and 20 and 45 (CVD, cog and SES)
49. 14 and 32 (CVD and IQ)
50. 14 and 36 (CVD and education)
51. 14 and 45 (CVD and SES)
52. 46 or 47 or 48 (CVD, Cog and any early life factor)
53. 49 or 50 or 51 (CVD and any early life factor)
54. 52 or 53

NOTE: This search strategy was developed to identify studies examining early life factors (childhood/premorbid IQ, education and childhood SES) in relation to: a. Clinical and subclinical cerebrovascular disease b. Cognitive impairment in those with clinical and subclinical cerebrovascular disease c. Depression in those with clinical and subclinical cerebrovascular disease. In order to answer several questions screening was performed to identify studies which addressed any of these topics. Papers not relevant to the topic of the current work are excluded.

Appendix 2B: Details of included studies and extracted results (statistics) used in the meta-analysis of early life risk factors and subclinical CVD

Study	Setting	Total N	Outcome - Present	Outcome - Absent	Age at MRI	Measure of early life factor	Primary outcome	Results	p
1a Cognitive ability									
PATH through life project	Community	446			60-64	Spot-The-Word Test	WMH (%)	Males: r=-0.03	p>0.05
(Christensen et al., 2007)							Computerised volumes validated by Fazekas	Females: r=-0.12	p>0.06
Scottish Mental Health Survey	Population cohort	83			78	Moray House Test aged 12	WMH	Pearson's correlation	
(Deary et al., 2003)							Fazekas scale	Total WMH: r=-0.028	p>0.05
								PVH: r= -0.050	p>0.05
								DWMH: r= 0.002	p>0.05
Aberdeen Birth Cohort 1936	Population cohort	243			68	Moray House Test aged 11	WMH	Spearman's correlation	
(Murray et al., 2014)							Scheltens scale	DWMH: r= -0.129	p>0.05
								PVH: r= -0.141	p<0.05
Aberdeen Birth Cohort 1921	Population cohort	106			78.3	Moray House Test aged 11	WMH	Pearson's correlation	
(Salarirad et al., 2011)							Scheltens scale	Total WMH: r=0.046	p>0.05
Lothian Birth Cohort 1936	Population cohort	634			73	Moray House Test aged 11	WMH (%)	β=-0.08	p<0.05

(Valdés Hernández et al., 2013a)							Fazekas scale	Pearson's correlation	
								PVH: r= -0.12	p<0.001
								DWMH:r= -0.05	p>0.05
								WMH % ICV: r= -0.07	p>0.05
1b Childhood socioeconomic status									
Aberdeen Birth Cohort 1936	Population cohort	243			68	Moray House Test age 11	WMH	Spearman's correlation	
(Murray et al., 2014)							Scheltens scale	DWMH: r= -0.181	p<0.01
								PVH: r= -0.146	p<0.05
1c Education									
White matter hyperintensities (WMH)									
The Framingham Heart Study: Offspring Cohort	Population Cohort	1820	1579	240	Approx. 61	<High school	WMH: None/non-large vs WMH - L (Large)	< HS: n = 60 vs 9	0.67
(Au et al., 2006)						High school		HS: n = 1519 vs 231	
Rotterdam Scan Study and Zoetemeer Study	Population Cohort	1077	1023	54	Approx. 70	≤ Primary school	WMH: Absent vs WMH Present	≤ PS: n = 673 vs 41	0.31
(de Groot et al., 2000)						> Primary school	Visually rated	> PS: n = 350 vs 13	
ARIC	Population Cohort	1920	280	1640	45-64	< High school	WMH: None vs mild/ moderate/severe	< HS: n=326 vs 212	
(Liao et al., 1997)						≥ High school	Visually rated	≥ HS: n=912 vs 470	
Esprit	Population Cohort	500	328	172	<80	Low education (≤ 8 years)	Graded WMH volume (Low: ≤	≤ 8 years: n= 92 vs 37	

(Mortamais et al., 2014)						High education (> 8 years)	0.3ml; vs mild/severe: >0.3ml)	> 8 years: n= 236 vs 135	
(Tsukishima et al., 2001)	Population Cohort	300	67	233	Approx. 70	< 6 years	WMH: Absent vs Present	OR: <6 years: 0.9 (0.3-2.8)*	
						≥ 6 years			
(Schretlen et al., 2007)	Community	177			Approx. 60	Years of education	WMH volume-PVH only Small/moderate vs large	OR: 0.87 (0.66-0.99)†	0.04
(Boone et al., 1992)	Community	100	54	46	45-83	Mean years of education	WMH: Absent vs Present (> 1cm; ≤ 10cm²)	WMH: Absent = 14.2 ±2.8	0.25
								WMH: >1-≤ 10cm² = 14.2±3.1	
The Epidemiology of Vascular Aging (EVA)	Population Cohort	845	521	320*	Approx. 69	Mean years of education	Graded WMH (mild vs moderate) Scheltens scale	WMH - Absent/Mild = 10.6±3.4	
(Dufouil et al., 2003)								WMH-Moderate = 10.8±3.5	
(Yamawaki et al., 2015)	Population	688	292 (DWMH)		76.5	Mean years of education	WMH (mild vs moderate)	PVH: Mild: 9.8±2.1	>0.05
			250 (PVH)					PVH: Moderate: 9.6±2.2	
							Fazekas scale	DWMH: Mild: 9.8±2.2	
								DWMH: Moderate: 9.7±2.3	

Northern Manhattan Study (NOMAS)	Population Cohort	259			Approx. 65	< High school	Mean WMH volume (log)	<HS: 0.36±0.08	
(Wright et al., 2005)						≥ High school		≥ HS: 0.37±0.09	
PATH Through Life Project	Population Cohort	446			Approx. 63	0-12 years	WMH density volume	0-12: 0.90±0.76	
(Christensen et al., 2009)						16+ years		16+: 0.78±0.72	
The Three City (3C) Study	Population Cohort	1792			Approx. 72	Low education (Primary Certificate Level 1 &2)	WM lesion volume (cm^3)	Low: 5.60±0.15	
(Godin et al., 2009)						High education (Baccalaureate or university degree)		High: 5.59±0.18	
Cardiovascular Health Study	Population Cohort	3622			65+	<High school	Mean WMH grade	< High school: 2.4±1.4	
(Elkins et al., 2006)						High School	Visually rated	≥ High school: 2.2±1.4	
Aberdeen Birth Cohort 1936	Population Cohort	243			Approx. 68	Best qualification obtained ranging from 1 (no qualifications) to 9 (professional or higher degree)	WMH	DWMH: r=-0.149	<0.05
(Murray et al., 2014)							Scheltens scale	PVH: r= -0.167	<0.05

(DeCarli et al., 2008)	Community Outpatient Clinic	401			>60	Years of education	WMH volume	F= 0.10	0.74
Gait and Alzheimer Interaction Tracking Study (GAIT)	Outpatient clinic	133			71.6	Low education (< Graduate studies)	WMH (Semi-quantitative visual rating scale 0-9). Fazekas scale	High education: Overall WMH: β= 0.43 (-0.29-1.15)‡	0.238
(Annweiler et al., 2014)						High education (≥ Graduate studies)		High education: DWMH: β= -0.01 (-0.37-0.35)‡	0.964
								High education: PVH: β= 0.08 (-0.21-0.36)‡	0.598
Small Vessel Disease (SVD)									
Brazilian Ageing Brain Study Group (BABSG)	Population Cohort	675			Approx. 74	No formal education	SVD (assessed in 13 areas)	No education: n = 56 vs 67	0.003
(Farfel et al, 2013)						Vs formal education	Absent vs mild-severe	Formal education: n = 314 vs 218	
PRESENT Study	Community	636	318	318	>64	<7 years	SVD (presence of SI and WMH)	No SVD: n= 60 vs 153	0.679
(Minn et al., 2013)						≥ 7years		SIVD: n= 60 vs 165	
(Tsukishima et al., 2001)	Population Cohort	300	67	233	Approx. 70	< 6 years	SVD (presence of WML and SI)	OR: 1.1 (0.4-1.3)*	
						≥ 6 years			
LADIS	Outpatient Clinic	639	89	524	Approx. 73	Mean years of education	SVD (presence of WML and lacunes)	No SVD: 9.8±3.7	0.022

(Jokinen et al., 2009)	Hospital							SVD: 8.8±9.8	
Mayo Clinic Study of Aging	Population	393	89	178	75-83	Median years of education	SVD (presence of cortical or subcortical infarct and/or WMH)	SVD: 14 (12-16)	
(Vemuri et al., 2015)								No SVD: 13.5 (12-16)	
(Sims et al., 2014)	Community	172			Approx. 64	≤ High school	SVD (presence of SI and WMH)	β=-0.258§	0.01
						> High school			
Lacunes									
Brazilian Ageing Brain Study Group (BABSG)	Population Cohort	675			Approx. 74	No formal education vs	Lacunes: Absent vs present	No formal education: n= 82 vs 48	0.44
(Farfel et al, 2013)						Formal education		Formal education: n= 383 vs 162	
EClipSE	Population	790	186	604	>65	0-3 years	Lacunes: Absent vs present	0-3 years: n = 39 vs 20	
(Brayne et al., 2010)	Autopsy					> 3 years		>3 years: n= 565 vs 166	

Appendix 2C: Details of included studies and extracted results (statistics) used in the meta-analysis of early life risk factors and stroke

1a Education									
Study	**Setting**	**Total number of participants**	**Participants with stroke (n)**	**Participants without stroke (n)**	**Age at follow up/stroke**	**Measure of education**	**Primary outcome**	**Measurement of outcome**	**Results**
Mean years of education									
(Tatemichi et al., 1992)	Hospital Outpatient clinic	500	251	249	71.9	Mean years of education	Ischaemic stroke	Clinical examination Neuroimaging	Stroke: 10.1±4.5 Non-stroke: 12.3±4.6
Sydney Stroke Study (Sachdev et al., 2014) 3-7	Hospital	280	183	97	71.91	Mean years of education	Ischaemic stroke and TIA	Clinical examination Neuroimaging	Stroke: 10.10±2.66 Non-stroke: 11.75±3.31

(Lukatela et al., 2000)	Outpatient clinic	218	159 89 Single stroke 70 Multiple infarction	59	Mean age approx. 72	Mean years of education	Ischaemic and haemorrhagic stroke	Clinical examination Neuroimaging	Single stroke: 11.97±2.57 Multiple infarction: 11.62±3.23 Non-stroke: 12.86±2.51
Vantaa 85+ Study (Rastas et al., 2007)	Population	553	111	442	88.5	Mean years of education	Ischaemic, haemorrhagic stroke and TIA	Clinical examination Centralised Health Statistics	Stroke: 3.2±2.0 Non-stroke: 4.3±3.0
(Copstein et al., 2013)	Population	3,391	285	3,106	≥20 44.13 (whole sample)	Mean years of education	Ischaemic and haemorrhagic stroke	Self-report questionnaire	Stroke: 7.09±4.05 Non-stroke: 8.12±3.45
Honolulu- Asia Aging Study	Population	3,734	147	3,170	78.8	Mean years of education	Ischaemic and	Neuroimaging	Stroke: 9.8±3.0

(Petrovitch et al., 1998)							haemorrhagic stroke	Case note review	Non-stroke: 10.5±3.2
(Mok et al., 2004)	Hospital	117	75	42	71	Mean years of education	Ischaemic stroke and TIA	Clinical examination Neuroimaging	Stroke: 4.8±4.1 Non-stroke: 5.4±4.6
(Hochstenbach et al., 1998)	Hospital	262	229	33	18-70 mean = 55.9	Mean years of education	Ischaemic and haemorrhagic stroke	Clinical examination Neuroimaging	Stroke: 4.1±1.5 Non-stroke: 4.4±1.5
Helsinki Stroke Aging Memory (SAM) Study (Jokinen et al., 2006)	Hospital	361	323 85 Subcortical ischaemic	38	71.7	Mean years of education	Ischaemic stroke	Clinical examination Neuroimaging	Stroke (other): 9.8±4.3 Non-stroke: 9.4±3.5

			vascular disease 238 other stroke						
(Kastorini et al., 2013)	Hospital	500	250	250	77/73	Mean years of education	Ischaemic stroke	Clinical examination Neuroimaging	Stroke: 8±4.6 Non-stroke: 8±4.9
Third National Health and Nutrition Survey (NHANES III) (Bravata et al., 2005) 17-19	Population	11,163	619	10,544	>40 Average <65	Year of schooling	Ischaemic and haemorrhagic stroke	Self-report questionnaire	Stroke: 9.2±4.1 Non-stroke: 10.3±4.2
(Kauranen et al., 2013)	Hospital	190	140	50	52	Mean years of education	Ischaemic stroke	Clinical examination Neuroimaging	Stroke: 12.5±2.6 Non-stroke: 12.4±2.9
(Reitz et al., 2006)	Community	1,271	97	1,174	76.3	Mean years of education	Ischaemic, haemorrhagic stroke and TIA	Clinical examination	Stroke: 8.9±4.3

							WHO criteria	Neuroimaging Case note review Self-report questionnaire	Non-stroke: 8.6±4.6
(Gillespie et al., 2012)	Hospital	112	56	56	40-88 65.55	Mean years of education	Ischaemic and haemorrhagic stroke	Clinical examination Neuroimaging	Stroke: 10.09±1.64 Non-stroke: 10.56±2.12
(Kessels et al., 2006)	Hospital Outpatient Clinic	266	105	161	59.5	Mean years of education	Ischaemic and haemorrhagic stroke	Clinical examination	Stroke: 10.7±3.7 Non-stroke: 10.3±3.2
Columbia-Presbyterian Medical Centre (Desmond et al., 2002)	Outpatient Clinic	575	334	241	≥60	Mean years of education	Ischaemic stroke	Clinical examination Neuroimaging	Stroke: 10.2±4.6 Non-stroke: 12.5±4.4

25									
Frequencies (n=stroke vs without stroke)									
(Hu et al., 2005)	Population cohort	47,721	2,863	44,858	Men: 49.5 Women: 52 No range	0-6 years 7-9 years 9+ years	Ischaemic and haemorrhagic stroke	Centralised Health Statistics	0-6 years = 798 vs 12,610 ≥7 years = 2,065 vs 32,248§
Japan Public Health Centre-based Prospective Study (JPHC) (Honjo et al., 2009) 28-30	Population cohort	29,134	793	28,341	50-69	Age at completion of education ≤ 14 years 15-17 years	Ischaemic and haemorrhagic stroke	Neuroimaging Case note review Centralised health statistics Self-report	≤ 14 years = 439 vs 13,662 ≥15-17 = 354 vs 14,679§
National Health Interview Survey (NHIS-1994)	Population cohort	11,925	71	11,854	All ages included	Not educated (NE)	Ischaemic and haemorrhagic stroke	Case note review	≤ PS = 60 vs 5,459§

(Huang et al., 1997)					Majority over 65yrs	Primary school (PS) ≥ Junior School (JS)		Self-report	≥ JS = 11 vs 6,395
Framingham Heart Study (Weinstein et al., 2014) [33]	Population cohort	264	132	132	77.4	< High school (<HS) High school degree (HS) Some college ≥ College degree	Ischaemic and haemorrhagic stroke	Clinical examination Neuroimaging Case-note review Centralised Health Statistics Self-report	<HS =14 vs 10 ≥ HS = 118 vs 122§
Health and Aging and Body Composition (Health ABC) (Koster et al., 2005)	Population cohort	2,574	180	2,394	70-75	< 12 years 12 years >12 years	Ischaemic, haemorrhagic stroke and TIA	Clinical examination Self-report	<12 years = 82 vs 1,046 ≥ 12 years = 98 vs 1,345§

REGARDS (Brenner et al., 2010)	Population cohort	27,716	2,830	24,886	≥45 Majority over 65yrs	< High school (<HS) High school degree (HS) Some college (SC) College graduate (CG)	Ischaemic, haemorrhagic stroke and TIA	Self-report	<HS = 611 vs 2,986 ≥ HS = 2,216 vs 21,924§
(de Bruijn et al., 2014)	Hospital	157	96 94 with education	61	47.3 18-49	Low: ≤ High school (HS) Medium: Secondary vocational education High: ≥Higher professional or university	Ischaemic stroke	Clinical examination Neuroimaging	≤ HS = 35 vs 7 >HS = 59 vs 54§
Multi-ethnic Study of Atherosclerosis (MESA)	Outpatient clinic	6,749	195	6,554	68.3	<High school (<HS)	Ischaemic, haemorrhagic stroke and TIA	Clinical examination	<HS = 43 vs 1,171

(Everson-Rose et al., 2014)			147 strokes 48 TIA		45-84	High school or some college (HS) ≥College degree (≥CD)		Neuroimaging	≥HS = 152 vs 5,383§
Uppsala Longitudinal Study of Adult Men (ULSAM) (Wiberg et al., 2012)	Population cohort	919	155 72 with education	764 729 with education	70	Elementary school (6-8 years) Secondary school (12 years) ≥College (>12 years)	Ischaemic, haemorrhagic stroke and TIA	Centralised health Statistics Medical records	6-8 years = 53 vs 571 ≥12 years = 19 vs 158§
EPIC- Postdam Study (Weikert et al., 2008)	Population cohort	27,548	168 167 with education	2,198 2,196 with education	55.9 35-65	≤ Vocational school (≤ 10 years) Technical school (12 years) University (>12 years)	Ischaemic stroke	Case note review Self-report questionnaire Death certificate	≤ 10 years = 72 vs 808 ≥12 years: n = 95 vs 1,389§

Cardiovascular Health Study (Yan et al., 2013)	Cohort study	4,619	650	3,969	≥65 73.57	<High school (<HS) High School or GED (HS) Some college (SC) College graduate (CG) Graduate or Professional school (Grad)	Ischaemic stroke	Clinical examination Centralised Health Statistics Self-report	<HS = 216 vs 1125 ≥HS = 434 vs 2,844§
Diet, Cancer and Health Danish Follow up Study (Nybo et al., 2008)	Hospital	508	254	254	60.5 50-64	7 years 8-10 years >10 years	Ischaemic stroke	Neuroimaging Centralised Health Statistics Autopsy	≤ 10 years = 217 vs 203§ >10 year =37 vs 51
(Engels et al., 2014)	Population	44,742	127	44,615	15+	0-4 years	Ischaemic and haemorrhagic stroke	Clinical examination	0-9 = 117 vs 33,716§

					Majority of stroke over 65yrs	5-9 years ≥10 years		Neuroimaging Self-report	≥10: n=10 vs 10,899
(Trygged et al., 2011)	Population	424,281	42,026	382,255	18-64	Compulsory (9 years) Upper Secondary University	NS	Centralised Health Statistics	Compulsory = 16,642 vs 126,482 ≥ Upper secondary = 25,359 vs 255,798§
Social Inequality in Cancer Cohort Study Combines Copenhagen City Heart Study, 1936 Cohort Study, Monica I, II, III, Diet Cancer and Health Study and Inter 99 Study	Population cohort	68,643	3,613	65,030	30-70 54 at baseline (follow up 14 years)	Low: Primary and lower Secondary Medium: Upper secondary, vocational or technical education	Ischaemic stroke	Centralised Health Statistics	Low = 1,393 vs 67,250 ≥Medium = 2,148 vs 135,066§

(Nordahl et al., 2014)						High: University			
(Valko et al., 2008)	Hospital	689	235 214 with education	454 447 with education	63/47 21-87	Primary school (PS) Secondary school (SS) College (Coll) University (Uni)	Ischaemic stroke	NS	PS = 59 vs 43 ≥ SS = 155 vs 404§
Assets and Health Dynamics among the oldest old (AHEAD) (Wolinsky et al., 2009)	Population	5,511	545	4,966	≥65	Grade school (GS) High school (HS) College (Coll)	Ischaemic and haemorrhagic stroke	Centralised Health Statistics	GS = 137 vs 1,241 ≥ HS = 408 vs 3,725§
(Baune and Aljeesh, 2006)	Hospital	336	112	224	35-69	No education	Ischaemic and haemorrhagic stroke	Clinical examination	≤ Prep = 86 vs 157

	Outpatient clinic		111 with education	223 with education	Majority under 65yrs	Primary school (PS) Preparatory school (Prep) Secondary school (SS) University degree (Uni) Other		Neuroimaging	≥ SS = 25 vs 66§
(Deoke et al., 2012)	Hospital	201	101	100	59.3 Most over 60	Illiterate or Primary school (≤ PS) >Primary school (>PS)	Ischaemic and haemorrhagic stroke	Clinical examination Neuroimaging	≤ PS = 38 vs 34 >PS = 63 vs 66
Oxford Vascular Study (OXVASC) Oxford Project to Investigate Memory and Ageing (OPTIMA)	Population	314	207	107	71.4	<12 years ≥12 years	Ischaemic and haemorrhagic stroke	NS	<12 years = 119 vs 25 ≥12 years = 88 vs 82

(Pendlebury et al., 2012)									
Kingsholem Project (Zhu et al., 2000)	Population	1,301	183	1,118	≥75	<8 years ≥8 years	Ischaemic and haemorrhagic stroke	Centralised Health Statistics Hospital register	<8 years = 96 vs 559 ≥8 years = 87 vs 559
(Sim et al., 2008)	Outpatient clinic Population	479	265	214	58.87 40-79	<12 years ≥ 12 years	Ischaemic and haemorrhagic stroke	Clinical examination	<12 years = 141 vs 117 ≥ 12 years = 124 vs 97
Swedish military service conscription (Wennerstad et al., 2010)	Population	1,135,383	8,215	1,127,168	NS 28-55	≤ 9 years > 9 years	Ischaemic and haemorrhagic stroke	Centralised Health Statistics Cause of death register	≤ 9 years = 1,945 vs 157,804 >9 years = 6,270 vs 969,364

[55]								ICD 8 : 430-438; ICD 9: 430-435, 437; ICD10: I60, I62-I69, G45	
CogFAST Nigeria Study (Akinyemi et al., 2014)	Out-patient clinic Hospital	219	143	74	≥45 60.4	None (0 years) Primary education (1-6 years) Secondary education (7-12 years) Tertiary education (>12 years)	Ischaemic and haemorrhagic stroke	Clinical examination and neuroimaging WHO criteria	0-6 years = 60 vs 21§ ≥ 7 years = 83 vs 53§
(Liu and Xie, 2008)	Hospital	112	60	52	73	Illiterate	Ischaemic stroke	Clinical examination	≤ PS = 30 vs 37§

						Primary school (PS; 0-6 years) Middle school (MS;7+ years)		Neuroimaging Chinese classification - 1995	> MS = 30 vs 15
Odds Ratios									
Jilin Provincial Chronic Disease Survey of 2012 (Wang et al., 2015)	Population	21,435	NS	NS	18-79 Majority under 60yrs	≤ Primary school Junior high school Senior high school ≥ College	"Cerebrovascular disease" Based on the ICD10: I60-67, I69	Self-report questionnaire	OR = 0.91 (0.78-1.07)*†

(Iliff et al., 2014)	Population	512,891	8,884	504,007	35-74 61.5	No formal school Primary school (PS) Middle school (MS) High school (HS) College/university	Ischaemic, haemorrhagic stroke and TIA	Self-report questionnaire	OR = 2.28 (2.02-2.56)*†
(Hamano et al., 2014)	Population	326,229	4,718	321,511	≥30	Compulsory school (≤ 9 years) High school (10-12 years) High school/college (>12 years)	Ischaemic and haemorrhagic stroke ICD10: I60-I69	Centralised Health Statistics	OR = 1.56 (1.45-1.67)†
(Strodl and Kenardy, 2008)	Community	7,839	174	8,939	70-75	No formal education Primary school (PS)	Stroke	Self-report questionnaire	OR = 0.98 (0.68-1.41)*

						Secondary school (SS) Tertiary			
Nanjing Chronic Disease and Risk Behaviour Study (NCDRBS) (Xu et al., 2008)	Population	29,340	453	28,887	>35 Majority of stroke >65	0-9 years 10-12 years >13 years	Stroke WHO MONICA	Self-report questionnaire Medical records	OR = 1.08 (0.82-1.44)*†
(Medin et al., 2008)	Hospital	168	65	103	54.8	Low education (6-9 years) High education (> 9 years)	Ischaemic and haemorrhagic stroke ICD10 I61, I63, I64	NS	OR = 2.48 (1.18-5.23)†
(You et al., 1999)	Community and hospital	904	452	452	59	No high school Some high school	Ischaemic stroke WHO classification	NS	OR = 0.83 (0.47-1.47)*†

						Completed high school Other tertiary University			
(Kisjanto et al., 2005)	Hospital	917	235	682	20-44	Illiterate or elementary school (ES) ≥Secondary school	Ischaemic and haemorrhagic stroke WHO classification	Clinical examination	OR= 0.72 (0.52-0.99)*
(Löfmark and Hammarström, 2007)	Population	55,266	457	54,809	35-85 Split into 35-75 and 75-85	Low education (maximum of 9 years compulsory school) High education (>9years compulsory school)	Ischaemic stroke WHO classification ICD 10: I63.0-I63.9	Centralised health Statistics	OR: Age 35-75 years = 1.09 (0.88-1.34)† OR: Age 75-85 years = 2.48 (1.06-5.77)†

(Folsom et al., 1990)	Population	2,063	218	1,845	55-69	<High school (<HS) High school (HS) >High school (>HS)	Ischaemic and haemorrhagic stroke ICD 9: 430-438	Centralised health Statistics Self-report questionnaire Contact with GP	OR = 0.6 (0.4-0.8)*†
The Rotterdam Study (Van Rossum et al., 1999)	Population	4,274	162 105 with history of stroke (HS) 157 with stroke at follow up (FS)	3,996 (baseline) 3,839 (follow up)	NS Majority over 65yrs	Primary school (PS) Lower/intermediate general and lower vocational education Higher general and intermediate	NS ICD 10	Case note review Centralised Health Statistics Self-report	OR: HS = 0.89 (054-1.49)*† OR: FS = 0.86 (0.57-1.30)*†

						vocational education Higher education (vocational) and university			
Vasterbotten Intervention Program (VIP) in collaboration with WHO MONICA (Resnick et al., 2003)	Population	1,148	473	945	25-74 54.7	Low (≤9 years) Medium (10-12 years) High (≥ 13 years)	Ischaemic and haemorrhagic stroke	Neuroimaging	OR: Men = 1.1 (0.7-1.8) OR: Women = 1.1 (0.7-1.9)
(Draganski et al., 2011)	Hospital	618	309	309	61.34/61.03	≤Junior school (≤JS)	Ischaemic stroke	Clinical examination	OR = 0.63 (0.42-0.96)*
(Fitzpatrick et al., 2012)	Population	1,612	401	1,211	52	Mean years of education	Ischaemic, haemorrhagic stroke and TIA	Self-report questionnaire	OR: 0.98 (0.93-1.04)*

Epidemiologic studies of the Elderly (EPESE) program (Fillenbaum et al., 2000)	Community	4,034	307	3,727	>65		NS	Self-report questionnaire	OR: 0.97 (0.95-1.01)*†
WHO collaborative study (Chang et al., 2002)	Hospital	8,146	2,162	5,984	15-49	High (>Secondary schooling) Secondary schooling Low (Primary or no schooling)	Ischaemic and haemorrhagic stroke Only Ischaemic stroke results used	Clinical examination	OR: Eastern Europe = 2.05 (0.92-4.54)† OR: Asia = 1.19 (0.71-1.98)† OR: Latin American = 1.16 (0.72-1.87)†
The Brain Attack Surveillance in Corpus Christie (BASIC) project	Population	1,147	808	339	≥45	<High school (<HS)	Ischaemic and haemorrhagic stroke and TIA	Case note review	OR: NHW = 4.53 (2.20-9.32)†

(Smith et al., 2003)			405 Non-Hispanic whites (NHW) 403 Mexican Americans (MA)		70	≥High school (≥HS)		Centralised health Statistics	OR: MA = 5.08 (3.17-8.14)†
(Jackson et al., 2014a)	Population	11,468	177	11,291	47-52	No formal education School certificate High school certificate Trades and apprentice Certificate/diploma University degree or higher	Ischaemic and haemorrhagic stroke ICD10: I60-I60.9, I61-I61.9, I53-I63.9 and I64	Self-report questionnaire Centralised health Statistics	OR = 1.30 (0.72-2.34)†

(Grau et al., 2012)	Hospital	740	370	370	60.7	≥ 12 years <12 years	Ischaemic, haemorrhagic stroke and TIA	Clinical examination Neuroimaging	OR = 0.81 (0.50-1.31)*†
Relative Risk									
(Andersen et al., 2014)	Population	54,048	NS	NS	71.9	Basic/High school (7-12 years) Vocational (10-12 years) Higher (≥13 years)	Ischaemic stroke	Neuroimaging Centralised health Statistics	RR = 0.99 (0.97-1.0)*†
NHANES I and NHEFS (Gillum and Mussolino, 2003)	Population	5,614	802	4,812	45-74 Majority of strokes >65	<8 years 8-11 years 12 years	Ischaemic and haemorrhagic stroke ICD 9: 431-434.9, 436, 437-437.1	Centralised health Statistics	RR: White Men =0.96 (0.73-1.27)*† RR: White Women = 0.91 (0.69-1.19)*† RR: Black Men and Women = 0.66 (0.46-0.96)*†

						>12 years			
(Lindenstrøm et al., 1993)	Population	13,000	696	12,304	>35 61.7	≤ 7 years ≥ 8 years	Ischaemic stroke and TIA	NS	RR = 1.3 (1.1-1.5)†
The Brain Attack Surveillance in Corpus Christie (BASIC) project (Lisabeth et al., 2007)	Population	631	631	NS	72.7	High school (HS) <High school (<HS)	Ischaemic and haemorrhagic stroke ICD 9: 430-432, 435-439	Neuroimaging Case note review Centralised health Statistics	RR = 0.42 (0.35-0.50)*†
(Hart et al., 2000)	Community	5,765	416	5,349	35-64	Age at leaving full time education: ≤ 16 Age at leaving full time education: >16	Ischaemic, haemorrhagic stroke and TIA ICD 8 & 9: 430-438; ICD 10: I60-I69, G45	Centralised health Statistics Hospital discharge records	RR = 1.28 (0.96-1.07)†
Hazard Ratios									

Kuopic Ischaemic Heart Disease Study (KIHD) (Everson et al., 2001)	Population	2,303	113 90 ischaemic	2,190	42-60	≤ Primary school (≤ PS/6 years) < High school/some vocational training (<HS/7-8 years) Some high school or more (≥ 9 years)	Ischaemic and haemorrhagic stroke ICD 9: 430-438 Only Ischaemic stroke results used	Centralised health Statistics FINMONICA stroke register	HR: 1.76 (0.87-3.55)
Malmo-Diet-and-Cancer-Cohort (Hamrefors et al., 2014)	Population	24,944	1,253	23,691	Approx. mean age of 58	Didn't complete elementary school Elementary school (6-8 years) Junior school (9-10 years) Education at advanced level (12 years)	Ischaemic stroke ICD9: 430, 431, 434, 436 ICD10: I60, I61, I63, I64	Centralised health Statistics	HR = 0.38 (0.23-0.62)*†

						At least one additional year University degree			
Northern Manhattan Stroke Study (NOMAS) (Boden-Albala et al., 2012)	Population	1,840	687	1,153	68.2	<High school (<HS) ≥ High school (≥HS)	Ischaemic stroke	Centralised health Statistics Self-report questionnaire	HR = 1.4 (1.1-1.7)†
Prevention with Mediterranean Diet (PREDIMED) (Mejía-Lancheros et al., 2014)	Outpatient clinics	7,263	136	7,126	55-80 67	Low education (Primary school education or less) High education (Secondary or university studies)	Ischaemic and haemorrhagic stroke	Case note review Self-report questionnaire	HR = 1.83 (1.09-3.09)†

								Centralised health statistics	
ARIC (Huxley et al., 2014)	Population	274,299	988	14,419	45-64	< High school High school graduate and/or vocational school College Graduate or professional school	Ischaemic and haemorrhagic stroke	Neuroimaging Case note review Centralised health statistics Self-report questionnaire	HR: black ethnicity = 1.79 (1.06-3.02)† HR: White ethnicity = 0.83 (0.56-1.23)†
Swedish Conscription Surveys	Population	44,495	592	43,903	40-55	≤9 years	Ischaemic and haemorrhagic stroke	Centralised health statistics	HR: 1.04 (0.99-1.09)

(Hemmingsson et al., 2007)						10-11 years 12-13 years 14 years ≥15 years	ICD 9: 430-438; ICD 10: I60-I69		
EPESE Newhaven sample (Avendano et al., 2006)	Population	2,494	260	2,234	≥65	0-7 years 8-9 years 10-12 years ≥13	Ischaemic and haemorrhagic stroke	Case note review Centralised health statistics Self-report/ questionnaire	HR =1.31 (0.66-2.65)†
Prospective population study of women in Gothenberg (Blomstrand et al., 2014)	Population	1,460	184	1,276	38-60	8 levels from elementary school to secondary school.	Ischaemic and haemorrhagic stroke Only Ischaemic stroke results used	Centralised health statistics	HR = 1.17 (1.01-1.35)†

Dutch National Survey of General Practice Avendano et al (2006)[100]	Population	190,665	472	190,193	≥25 70.9 (men);76.1 (females)	Low (no schooling or solely elementary education) Middle (Secondary schooling) High (Post-secondary education)	Ischaemic, haemorrhagic stroke and TIA International classification of Primary care coding system	Case note review	HR: Men = 1.58 (1.07-2.36)† HR: Women = 1.05 (0.59-2.14)†
Health and Retirement Study merged with Study of Asset and Health Dynamics among the Oldest Old; Children of the Depression; War Baby; Early Baby Boomer	Population	22,847	2,298	20,549	>51	Low: < High School (<9 years)	Ischaemic and haemorrhagic stroke	Self-report questionnaire	HR = 1.37 (1.17-1.59)†

(Liu et al., 2013)					Majority of strokes over 65yrs	Middle: High School (9-12 years) High: College (≥13 years)			
(Kuper et al., 2007)	Population	47,942	200	47,742	30-49	Total years of education	Ischaemic and haemorrhagic stroke ICD 9: 434, 431; ICD 10: I63.3- I63.9, I64; ICD 7: 332, 331; ICD 8: 433-434, 334 Only Ischaemic stroke results used	Centralised health statistics	HR = 2.2 (1.3-3.7)†

Jichi Medical School Cohort Study (Honjo et al., 2010)	Population	10,640	362	10,278	NS	Age at leaving school: ≤ 14 15-17 years ≥ 18 years	Ischaemic and haemorrhagic stroke	Clinical examination Neuroimaging	Males: HR: 0.92 (0.51-1.65)* Females: :HR: 1.04 (0.47-2.31)*
POSPECT and MORGEN (Méjean et al., 2013)	Population cohort	33,106	531	32,575	20-70 all mean ages are below 60	Lowest (Primary education) Lower (Intermediate, secondary or lower vocational) Higher (higher general or intermediate vocational) Highest (University or higher	Ischaemic and haemorrhagic stroke	Centralised health statistics ICD 9: 430-434, 436; ICD 10: I60-I66	HR = 1.21 (0.91-1.60)†

						vocational education)			
Prevalence Ratio									
(de Jesús Llibre et al., 2010)	Population	3,015	229	2,786	≥ 65	≤ 6 grades ≥ 7 grades	Ischaemic and haemorrhagic stroke WHO definition	Neuroimaging Self-report questionnaire	≥ 7 grades: Prevalence ratio: 0.90 (0.6-1.1)
1b. Childhood SES									
Study	**Setting**	**Total number of participants**	**Participants with stroke (n)**	**Participants without stroke (n)**	**Age at follow up/stroke**	**Measure of childhood SES**	**Primary outcome**	**Measurement of outcome**	**Results**
Hazard ratios									
Health and Retirement Study (Liu et al., 2013) 103, 109-111	Population Cohort	22,847	2,298	20,549	61	Sum of parents education	Ischaemic or haemorrhagic stroke	Clinical examination Neuroimaging	HR=1.35 (1.15-1.59)

Swedish Conscript Study 1949-1951 (Hemmingsson et al., 2007)	Population	44,495	592	43,903	40-55	Father's occupation Crowded housing	Ischaemic or haemorrhagic stroke	Centralised health statistics	HR= 1.08 (1.03-1.09)
Copenhagen City Heart Study (Kornerup et al., 2010)	Population	9,542	350	9,192	NS	Financial problems in childhood	Ischaemic stroke	Centralised health statistics	HR=1.71 (1.29-2.26)†
Frequencies (n=stroke vs without stroke)									
ARIC (Johnson et al., 2010)	Population Cohort	5,347	234 104 with childhood SES	5,113 2,507 with childhood SES	51.8 57-79	Father's education	Ischaemic stroke	Centralised health statistics Self-report	Low SES= 74 vs 1,736 High SES = 30 vs 875
(Hart et al., 2000)	Community sample	5,765	416	5,349	35-64	Father's occupation	Ischaemic, haemorrhagic stroke or TIA	Centralised health statistics	Low SES = 335 vs 3,948

			404 with childhood SES	5,249 with childhood SES					High SES = 69 vs 1,301
Nurse's Health Study Cohort (Gliksman et al., 1995)	Population sample	117,006	828 741 with childhood SES	116,178 40,947 with childhood SES	30-55	Father's occupation	Ischaemic or haemorrhagic stroke	Case note review Centralised health statistics	Low SES = 463 vs 63,697 High SES = 278 vs 40,947
British Regional Heart Study (Wannamethee et al., 1996)	Population cohort	5,934	136	5,380	40-59	Father's occupation	Stroke	Self-report	Low SES = 103 vs 3,903 High SES = 33 vs 1,477
Swedish Conscript Study 1951-1976 (Wennerstad et al., 2010)	Population cohort	1,135,383	8,215	1,127,168	Approx. 36	Father's occupation	Stroke	Centralised health statistics	Low SES = 4,580 vs 542,168 High SES = 3,635 vs 585,001
Odds Ratios									

(Grau et al., 2012)	Hospital	740	370	370	60.7 <80	Father's occupation	Ischaemic, haemorrhagic stroke or TIA	Clinical examination Neuroimaging	OR= 0.79 (0.48-1.30)*†
Prevalence Rate									
Aberdeen Children of the 1950's (Lawlor et al., 2006)	Population cohort	11,106	-	-	Approx. 50	Father's occupation	Ischaemic or haemorrhagic stroke	Centralised health statistics	PR per 10,000 PY: Social class I/II= 2.3 (1.0-6.9) PR per 10,000 PY: Social class V= 7.8 (5.6-11.3)
1c. Childhood/ Premorbid IQ									
Study	**Setting**	**Total number of participants**	**Participants with stroke (n)**	**Participants without stroke (n)**	**Age at follow up/stroke**	**Measure of childhood/ premorbid IQ**	**Primary outcome**	**Measurement of outcome**	**Results**
Hazard Ratios									
Danish Birth Cohort Study 1953	Population	6,910	93	6,817	≈ 47	Danish translation of the Swedish	Stroke	Centralised Health Statistics	HR=1.29 (0.75-2.25)†

(Batty et al., 2005)						Harnquist Intelligence Test	ICD 8: 430-438, 410-414 ICD 10: I60-I69, I20-25		
Swedish Conscription Study 1949-1951 (Hemmingsson et al., 2007)	Population	44,495	592	43,903	40-55	Standardised global IQ score	Ischaemic and haemorrhagic stroke ICD-9: 430–438 ICD-10: I60–I69	Centralised Health Statistics	HR = 1.26 (0.76-2.09)
Swedish Conscription Study 1951-1976 (Wennerstad et al., 2010)	Population	1,135,383	8,215	1,127,168	Mean age ≈ 36	Standardised global IQ score	Ischaemic or haemorrhagic stroke ICD8: 430-438 ICD9: 433-438	Centralised Health Statistics	HR=0.94 (0.92-0.96) *†

							ICD10: I60-I69, G45		
Helsinki Birth Cohort Study (Kajantie et al., 2012)	Population Cohort	2,786	131	2,655	56.7	The Finnish Defence Forces Basic Ability Test	Ischaemic or haemorrhagic stroke ICD8: 430-434, 436-437 ICD9: 430-434, 436-438 ICD10: I60-I69	Centralised Health Statistics	HR= 0.98 (0.75-1.27) †
Aberdeen Children of the 1950s (Lawlor et al., 2008)	Population Cohort	11,125	56	11,069	50-55	Moray House Test aged 11	Ischaemic or haemorrhagic stroke ICD9: 430-438 ICD10: I60-I69, G45	Centralised Health Statistics	HR=0.68 (0.55-0.84) *†
Mean Differences									
Sydney Stroke Study (Brodaty et al., 2010)	Hospital	264	167	97	72.42	NART-R IQ	Ischaemic stroke WHO criteria	Clinical examination	104.31 ± 10.26 Stroke 114.09 ± 7.99 Non-stroke

(Kessels et al., 2006)	Hospital	266	105	161	59.5	NART-R IQ	Ischaemic or haemorrhagic stroke	NS	97.1 ± 15.6 Stroke 101.1 ± 14.6 Non-stroke
(Sampson et al., 2003)	Hospital	103	50	49	72.5	NART-R IQ	Stroke	NS	105 (95-114) Stroke 110 (102-116) Non-stroke
Odds Ratios									
Wisconsin Longitudinal Study (Jokela et al., 2011)	Cohort	8,623	276	8,347	64.8	Henmon-Nelson Test of Mental Ability	Stroke	NS	OR=0.85 (0.74-0.99)†

* inverted for meta-analysis to demonstrate inverse relationship; † adjusted; § Sum of multiple categories to represent low and high education level

Appendix 2D: Details of included studies and extracted results (statistics) used in the meta-analysis of early life risk factors and post-stroke depression

Study	Setting	N	N with depression	N without depression	Age at follow up	Time post stroke	First stroke only	Measurement of stroke	Measure of early life factor	Measurement(s) of depression	Definition of depression	Previous depression excluded?	Results	p
COGNITIVE ABILITY														
(Brodaty et al., 2007)	Hospital	205	37	98	Depression: 73.3 No depression: 71.7	3 and/or 15 months	no	Clinical examination Neuroimaging	Mean score on the NART	DSMIV	Major depression: DSMIV	no	Depression: 101.84 ±9.83 No depression: 104.94 ±10.11	0.18
EDUCATION														
Correlation														
(Carod-Artal et al., 2009)	Rehab hospital	300	58	242	56.3 (14.3)	NS			Mean years	HADS	-		r= -0.25	<0.001
(Schreiner et al., 2001)	Outpatient clinic	101			Men- 54.5 Women- 69.9	45% ≤2 years			Duration in months	GDS-Short Form	-	yes	r= 0.105	>0.05
(Spalletta et al., 2002)	Hospital	153	RH-49 LH-39	RH-38 LH-27	MDD- RH-64.1/ 63.2 MDD- LH-67.8/69.7	≤1 year			Mean years	HADS SCID	- -		Right hem- r=-0.237 Left hem= r=0.087	0.03 0.49

(Visser et al., 2014)	Outpatient clinic	213				≥ 18 months			7 levels ranging from 1 (< Primary school) to 7 (University degree)	CES-D	-	no	r= 0.028* (spearmans rho)	
(Donnellan et al., 2016)	Hospital	64	20	44	61	ns	No	Clinical examination Neuroimaging	Mean years	HADS	- -	no	r= -0.34 (Pearsons)	≤ 0.01
Mean years														
(Brodaty et al., 2007)	Hospital	205	37	98	Depression: 73.3 No depression: 71.7	3 and/or 15 months	No	Clinical examination Neuroimaging	Mean years	DSMIV	Major depression : DSMIV	no	Depression: 10.39±2.65 No depression: 10.03±2.91	0.52
(Choi-Kwon et al., 2012)	Outpatient clinic	469	83	386	Depression: 63.2 No depression: 61.4	3 months	No	Neuroimaging	Mean years	BDI DSMIV	PSD: BDI >13 or Major depression : DSMIV	yes	Depression: 8.8 ± 4.9 No depression: 10.1 ± 5	<0.05
(Kim and Choi-Kwon, 2000)	Outpatient clinic	149	27	121	40-80 62	2-4 months	Yes	Clinical examination Neuroimaging	Mean years	DSMIV BDI	Major depression : DSMIV	yes	Depression: 10.5±4.7 No depression: 10.6 ± 4.7	
(Snaphaan et al., 2009)	Hospital	283	43	241	Depression: 64.9	ns	No	Clinical examination	Median years	HADS	Depressive symptoms >8	no	Depression: 4(1-7)	<0.01

					No depression: 65.9			Neuroimaging					No depression): 5 (1-7)	
(Starkstein et al., 1993)	Hospital	80	18	44	Depression:51.0 No depression: 61.1	10 days	Yes	Clinical examination Neuroimaging	Mean years	DSM-III PSE	Major depression : DSM-III	no	Depression: 9.9±2.9 No depression: 9.5±3.1	
(Tang et al., 2005)	Hospital	189	27	158	Depression: 67.3 No depression: 68.3	3 months	No	Clinical examination Neuroimaging	Mean years	SCID-DSM-IV	Major or minor depression : SCID-DSM-IV	no	Depression: 3.5±3.3 No depression:5 .5±4.8	0.04
(Tateno et al., 2002)	Hospital	354	73	281	Major depression: 58.2 Minor or no depression: 61.7	ns	No	Neuroimaging	Mean years	DSMIV HADS	Major depression : DSMIV	no	Major depression: 10±3.3 Minor or no depression: 10.1 ±3.9	
(Tene et al., 2016)	Hospital	306	45	261	Depressive episode: 68.2 No depression: 66.9	72 hours	No	Neuroimaging	Mean years	GDS	Depressive episode: GDS ≥6	no	Depressive episode: 11.8±3.2 No depression: 13.4±3.7	<0.05
Frequencies														
(Berg et al., 2001)	Outpatient clinic	100	24	65	55.2	2 weeks	Yes	Clinical examination Neuroimaging	≤ 8 years >8 years	BDI DSMIV	Mild depression : BDI ≥10	no	≤ 8 years: 9 vs 37 >8 years: 15 vs 28	0.10

(Fatoye et al., 2009)	Hospital	118	47	71	ns	Mean: 11 months	No	ns	None Primary school Secondary school Tertiary	BDI	Mild depression : BDI ≥10	no	<Secondary school: 34 vs 26 ≥Secondary school: 13 vs 45	0.001
(Hirata et al., 2016)	Population	546	87	459	Depression: 55.8 No depression: 65.8	Mixed	No	Self-report	< High school High school > High school	PHQ-8	Moderate depression : ≥10	no	<HS: 28 vs 134 ≥HS: 59 vs 325	
(Jiang et al., 2014)	Hospital	329	98	231	Depressive symptoms: 69.2 No depression: 66.6	2-6 weeks	No	Neuroimaging	Illiteracy Elementary school High school > High school	MADRAS DSMIV	Depressive symptoms: MADRAS ≥ 7	no	≤ High school: 73 vs 150 ≥ High school: 25 vs 81	
(Nys et al., 2006)	Hospital	91	48	43	Depression: 62.3 No depression: 60.8	6-10 months	Yes	Clinical examination Neuroimaging	7 levels ranging from 1 (< Primary school) to 7 (University degree) Dichotomised at the median	MADRAS	Depressive symptoms: MADRAS ≥7	yes	High education: 16 vs 22 Low education: 32 vs 21	0.09
(Paolucci et al., 2006)	Outpatient clinic	1,064	383	681	Depression: 67.4	Between 2-6 weeks	No	Neuroimaging	≤ 8 years	DSMIV BDI	Major depression : DSMIV	no	≤ 8 years: 86 vs 148	

					No depression: 67.1				> 8 years	Visual Analogue Dysphoria Scale	sad face'		>8 years: 297 vs 533	
(Shi et al., 2015)	Hospital	757	201	344	Early onset depression: 61.25 Late onset depression: 60.21 No depression: 61.07	2 weeks-1 year	Yes	Neuroimaging	<High school ≥High school	DSMIV	Major depression: DSMIV	no	<HS: 125 vs 220 ≥HS: 76 vs 124	
(Vataja et al., 2001)	Hospital	275	109	166	Depression: 70.3 No depression: 70.9	3-4 months	No	Clinical examination Neuroimaging	≤ 6 years >6 years	DSM-III-R PSE (10th edition)	Major depression: DSM-III-R	no	≤ 6 years: 32 vs 51 >6 years: 77 vs 115	0.56
(Verdelho et al., 2004)	Hospital	108	46	62	Depression: 69.5 No depression: 71	6 months	No	Neuroimaging	≤ Primary school >Primary school	MADRAS CAMDEX	Depressive symptoms: MADRAS ≥7	no	≤ Primary school: 38 vs 51 >Primary school: 8 vs 11	
(Li et al., 2002)	Hospital	126	76	50	Depression: 67.5 No depression: 69.8	ns	No	Clinical examination Neuroimaging	≤ 6 years >6 years	HDRS Chinese classification of mental disorders and diagnostic	HDRS ≥8 (mild depression)	no	≤ 6 years: 39 vs 13 >6 years: 37 vs 37	<0..01

										criteria 2nd edition				
(Zhang et al., 2009)	Community	276	180	96	67.5	Mean: 13 months	No	Clinical examination Neuroimaging	Illiteracy Primary school Middle school (8 years) >Middle school (>8 years)	Self-Rating Depression scale	mild depression	no	≤ Middle school: 147 vs 223 >Middle school: 33 vs 51	
(Zhang et al., 2005)	Hospital	312	135	177	ns	within 48 hours	No	Clinical examination Neuroimaging	Elementary school Middle school Junior college	HDRS	HDRS ≥8 (mild depression)	no	≤ Middle school: 86 vs 129 >Middle school: 49 vs 48	
Odds ratio														
(Altieri et al., 2012)	Hospital	105	43	62	64.4	1 month	No	ns	< 8 years ≥ 8 years	DSMIV	Major depression : DSM-IV	yes	OR: < 8 years vs ≥ 8 years: 1.6 (1.023-2.49)†	0.04
(Naess et al., 2005)	Population	NS	196	NS	15-49	Mean time: 6 years	Yes	Clinical examination Neuroimaging Centralised health statistics	Low/high education Not defined	MADRAS	Mild depression : MADRAS ≥7	no	OR: 1.33 (0.66-2.70)†	0.43
(Paul et al., 2013)	Population	241	113	128	Depression: 64.7 No depression: 60.8	Various	No	Clinical examination Self-report	Mean years	GDS (Bengali version)	Severe depression : GDS ≥21	no	OR: For every year decrease in education: 1.09 (1.02-1.17) §†	0.01

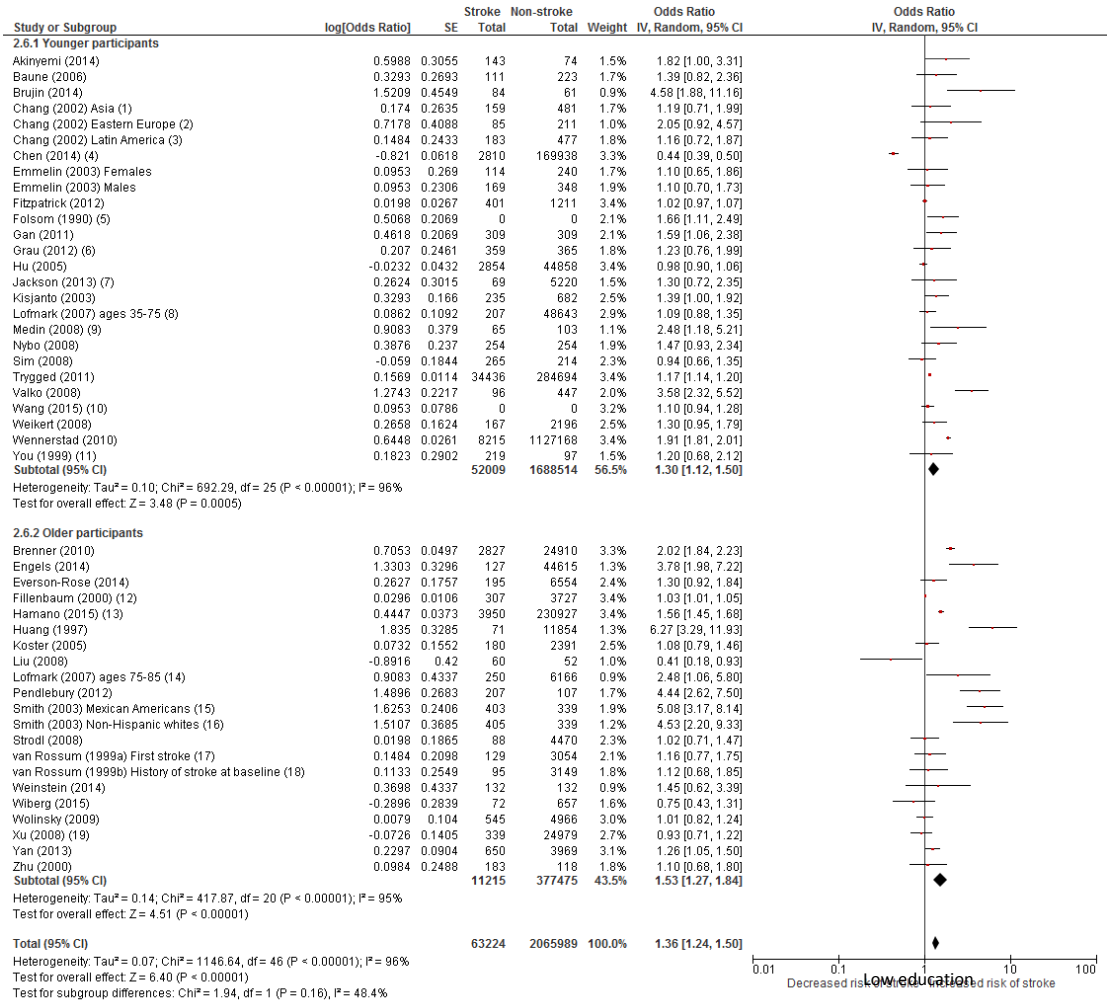
(Paolucci et al., 1999)	Hospital	470	129	341	66.26	Mean: 44.3 days	Yes	Clinical examination Neuroimaging Case note review	≤8 years > 8 years	HDRS Visual Analogue Dysphoria Scale	Severe depression : HDRS ≥18 Clinical picture of depressed mood at interview	yes	OR: <High school: 0.62 (0.40-0.96)≠†	0.03
(Schepers et al., 2009)	Hospital	131	33	98	56.3	1 year	Yes	ns	<University degree Higher professional or University degree	CES-D	Depressive episode: ≥16	no	OR: <University degree: 0.90 (0.36-2.26) †	0.83
(Sienkiewicz-Jarosz et al., 2010)	Hospital	242	82	160	Depression: 66.1 No depression: 65.2	3 months	Yes	Clinical examination Neuroimaging	≤ Primary school >Primary school	GDS	Depressive symptoms: GDS >5	no	OR: <Secondary school vs ≥Secondary school: 2.1 (1.2-3.8)	0.01
(Tang et al., 2011a)	Hospital	235	84	151	Depression: 67.1 No depression: 65.9	3 months	No	Clinical examination Neuroimaging	Years	GDS	Depressive symptoms: GDS≥7	yes	OR For every decrease in education: 1.04 (0.98-1.10) ¤†	0.25
(van de Port I.G.L. et al., 2007)	Hospital	165	31	134	57	3 years	Yes	Neuroimaging	<University education University education	CES-D	Depressive episode: CED-S ≥16	no	<University education: 1.56 (0.56-4.32) †	0.39

* adjusted for age, sex, income, smoking, age, cognitive dysfunction and activities of daily living

≠ adjusted for age, sex
§ adjusted for age, sex, income, smoking, age, cognitive dysfunction and activities of daily living
¤ adjusted for sex, lobar cerebral micro-bleeds, Lubben Social Network Scale score, Mini-Mental State Exam score, diabetes, National Institite of Health Stroke Scale score
† inverted for meta-analysis to demonstrate inverse relationship
DSM: Diagnostic Statistical Manual; BDI: Beck's Depression Inventory; HADS: Hospital Anxiety and Depression Scale; PSE: Present State Exam; HDRS: Hamilton Depression Rating Scale; GDS: Geriatric Depression Scale; PHQ: Patient Health Questionnaire; MADRAS: Montgomery-Asberg Depression Rating Scale; CES-D: Centre for Epidemiologic Studies Depression Scale; CAMDEX: The Cambridge Examination for Mental Disorders of the Elderly.

Appendices 2E-J: Sensitivity analyses on studies examining early life factors and stroke

Appendix 2E: Sensitivity analysis comparing studies that included younger (mean age ≤65 years) vs those that included older (mean age >65 years) participants by education level and risk of stroke; OR>1= low education increases risk of stroke.

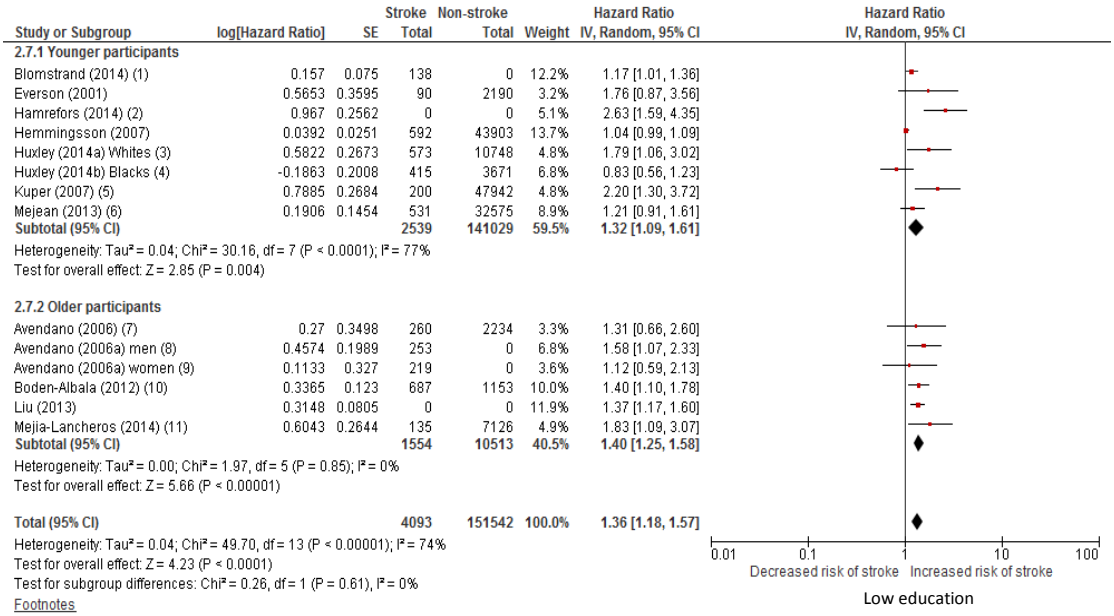


Footnotes

(1) Adjusted for history of high BP, use of oral contraceptives, marital status, number of live births, cigarette and alcohol consumption, hypertension in pregnancy, family history of premature stroke or AMI,...
(2) Adjusted for history of high BP, use of oral contraceptives, marital status, number of live births, cigarette and alcohol consumption, hypertension in pregnancy, family history of premature stroke or AMI,...
(3) Adjusted for history of high BP, use of oral contraceptives, marital status, number of live births, cigarette and alcohol consumption, hypertension in pregnancy, family history of premature stroke or AMI,...
(4) Adjusted for age,gender and region.
(5) Adjusted for age. Total number of strokes and controls for education categories used not specified. Total strokes and controls 218 and 1845 respectively.
(6) Adjusted for hypertension, diabetes, hyperlipidemia, previous stroke/TIA, and PAD, current smoking, alcohol abstinence, high alcohol consumption, leisure time sports activity
(7) Adjusted for age, home ownership, education, smoking, BMI, alcohol, physical activity, depression, marital status, hypertension, diabetes mellitus, heart disease and hysterectomy/oophorectomy
(8) Adjusted for age and sex
(9) Adjusted for work related factors on the Job Content Questionnaire, organisational change at the workplace and decreased participation
(10) Adjusted for age, gender, income, medical insurance, smoking and BMI.
(11) Adjusted for hypertension, heart disease, diabetes, smoking
(12) Adjusted for age, sex, race
(13) Adjusted for CHD, hypertension, COPD, obesity, income, age and sex.
(14) Adjusted for age and sex
(15) Adjusted for age and sex
(16) Adjusted for age and sex
(17) Adjusted for age, systolic BP, hypertension, drug use for hypertension, smoking, cardiovascular disease, left ventricular hypertrophy, atrial fibrilation, diabetes, fibrogen, BMI, alcohol consumption
(18) Adjusted for age, systolic BP, hypertension, drug use for hypertension, smoking, cardiovascular disease, left ventricular hypertrophy, atrial fibrilation, diabetes, fibrogen, BMI, alcohol consumption
(19) Adjusted for age, gender, area of residence, BMI, smoking, alcohol consumption, diabetes, high blood pressure, occupational and leisure time physical activity

NOTE: Studies without footnotes report unadjusted results

Appendix 2F: Sensitivity analysis comparing studies that included younger (mean age ≤65 years) vs studies that included older (mean age >65 years) participants by education level and risk of stroke; HR>1= low education increases risk of stroke.

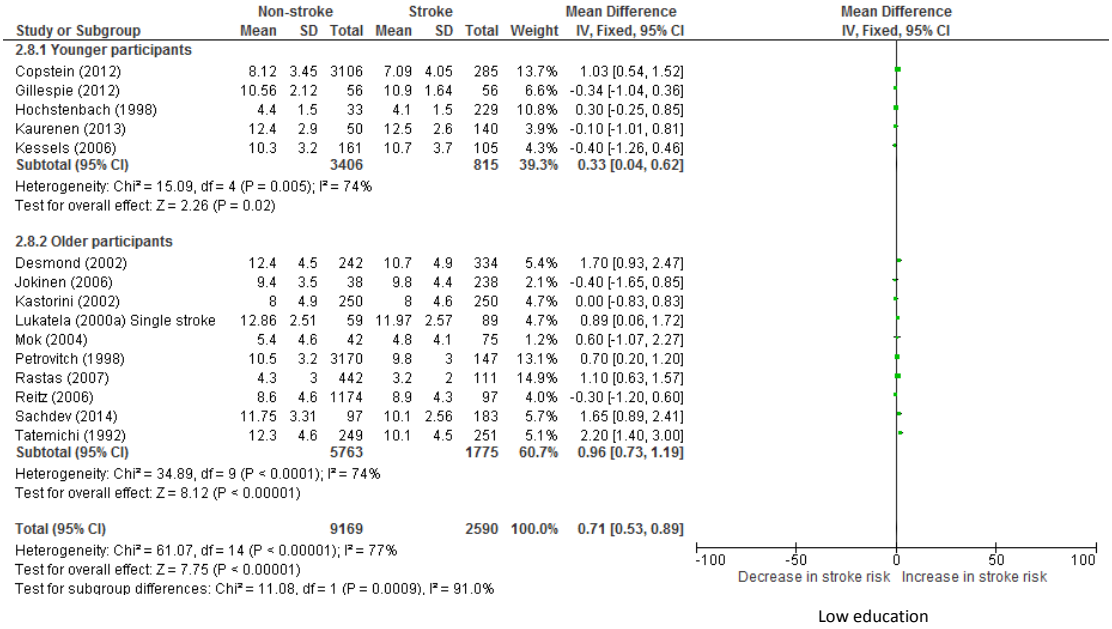


Footnotes

(1) Adjusted for age, hypertension, BMI, smoking, physical inactivity, cholesterol, tryglycerides, mental stress
(2) Adjusted for age and sex.
(3) Adjusted for age, sex, income, BMI, smoking, systolic blood pressure, antihypertensive medication, diabetes, HDL-C, LDL-C, lipid medication, CHD, PAD, ECG, carotid intima...
(4) Adjusted for age, sex, income, BMI, smoking, systolic blood pressure, antihypertensive medication, diabetes, HDL-C, LDL-C, lipid medication, CHD, PAD, ECG, carotid intima...
(5) Adjusted for age, smoking, BMI, alcohol consumption, hypertension, diabetes, exercise
(6) Adjusted for age, sex, physical activity, smoking, alcohol consumption, diet
(7) Adjusted for age, sex, race, sex, hypertension, smoking, diabetes, alcohol, BMI, physical activity, social networks, depression, difficult life events
(8) Adjusted for age
(9) Adjusted for age
(10) Adjusted for cardiac disease, hypertension, diabetes, inactivity, social isolation, Medicaid insurance, home heath aid.
(11) Adjusted for aged, gender, smoking, alcohol consumption, BMI, hypertension, diabetes, high cholesterol, family history of CHD and diet.

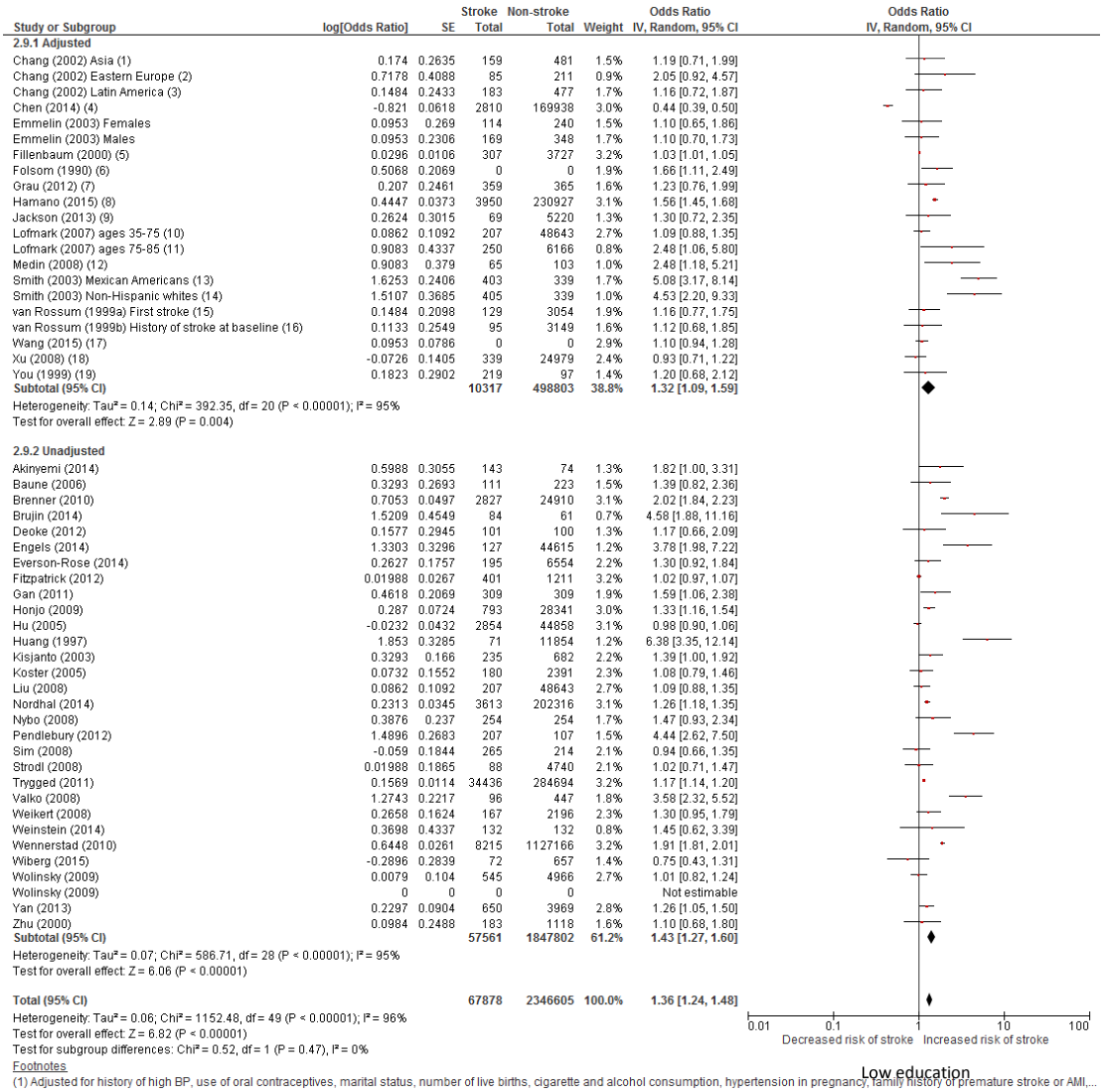
NOTE: Studies without footnotes report unadjusted results

Appendix 2G: Sensitivity analysis for comparing studies that included younger (mean age ≤65 years) vs studies that included older (mean age >65 years) participants by education level and risk of stroke; negative mean difference = lower education decreases risk of stroke and positive mean difference = lower education increases risk of stroke.



NOTE: Studies without footnotes report unadjusted results

Appendix 2H: Sensitivity analysis comparing adjusted vs unadjusted studies by education level and risk of stroke; OR>1= low education

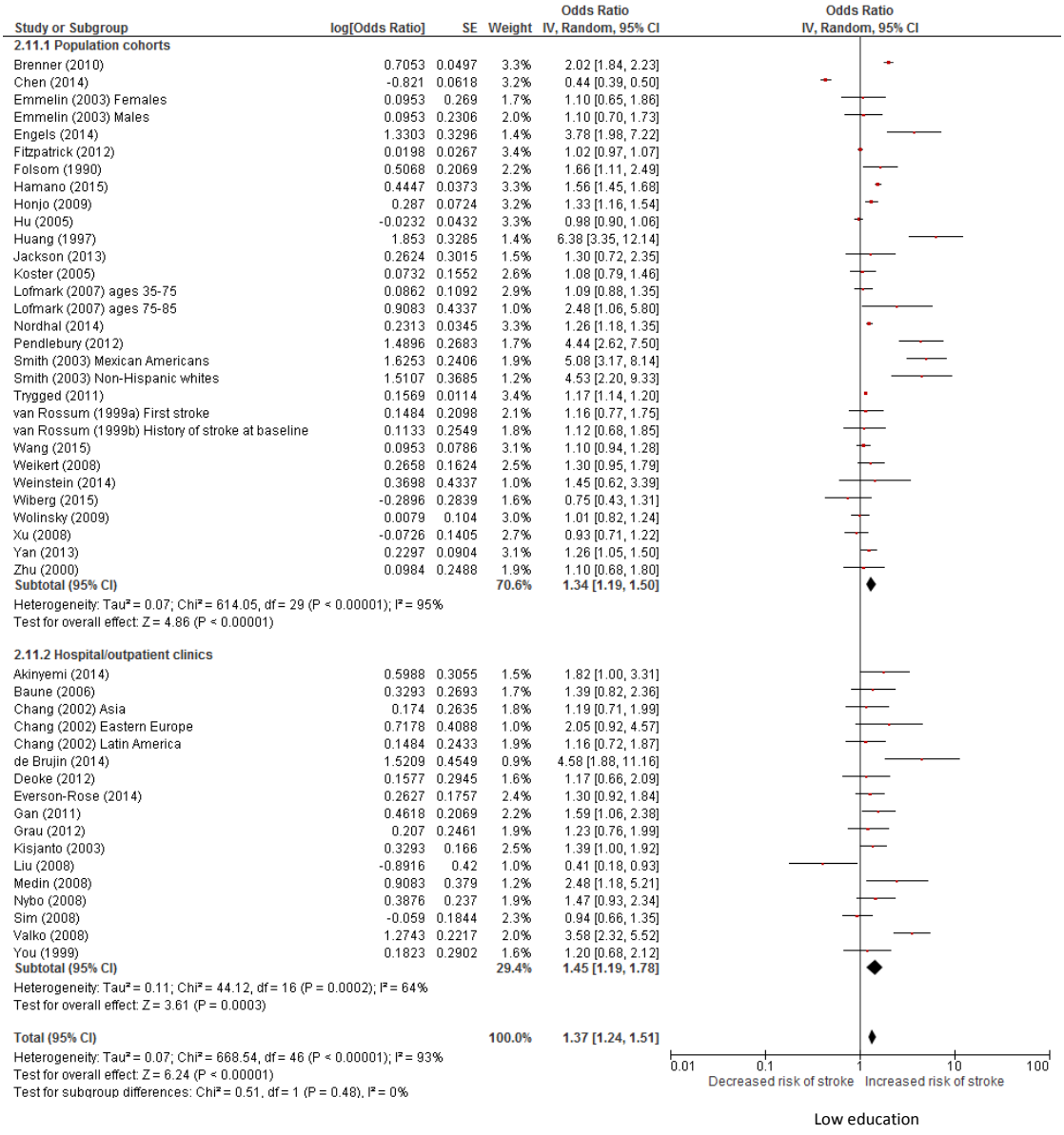


Footnotes

(1) Adjusted for history of high BP, use of oral contraceptives, marital status, number of live births, cigarette and alcohol consumption, hypertension in pregnancy, family history of premature stroke or AMI,...
(2) Adjusted for history of high BP, use of oral contraceptives, marital status, number of live births, cigarette and alcohol consumption, hypertension in pregnancy, family history of premature stroke or AMI,...
(3) Adjusted for history of high BP, use of oral contraceptives, marital status, number of live births, cigarette and alcohol consumption, hypertension in pregnancy, family history of premature stroke or AMI,...
(4) Adjusted for age,gender and region.
(5) Adjusted for age, sex, race
(6) Adjusted for age. Total number of strokes and controls for education categories used not specified. Total strokes and controls 218 and 1845 respectively.
(7) Adjusted for hypertension, diabetes, hyperlipidemia, previous stroke/TIA, and PAD, current smoking, alcohol abstinence, high alcohol consumption, leisure time sports activity
(8) Adjusted for CHD, hypertension, COPD, obesity, income, age and sex.
(9) Adjusted for age, home ownership, education, smoking, BMI, alcohol, physical activity, depression, marital status, hypertension, diabetes mellitus, heart disease and hysterectomy/oophorectomy
(10) Adjusted for age and sex
(11) Adjusted for age and sex
(12) Adjusted for work related factors on the Job Content Questionnaire, organisational change at the workplace and decreased participation
(13) Adjusted for age and sex
(14) Adjusted for age and sex
(15) Adjusted for age, systolic BP, hypertension, drug use for hypertension, smoking, cardiovascular disease, left ventricular hypertrophy, atrial fibrilation, diabetes, fibrogen, BMI, alcohol consumption
(16) Adjusted for age, systolic BP, hypertension, drug use for hypertension, smoking, cardiovascular disease, left ventricular hypertrophy, atrial fibrilation, diabetes, fibrogen, BMI, alcohol consumption
(17) Adjusted for age, gender, income, medical insurance, smoking and BMI.
(18) Adjusted for age, gender, area of residence, BMI, smoking, alcohol consumption, diabetes, high blood pressure, occupational and leisure time physical activity
(19) Adjusted for hypertension, heart disease, diabetes, smoking

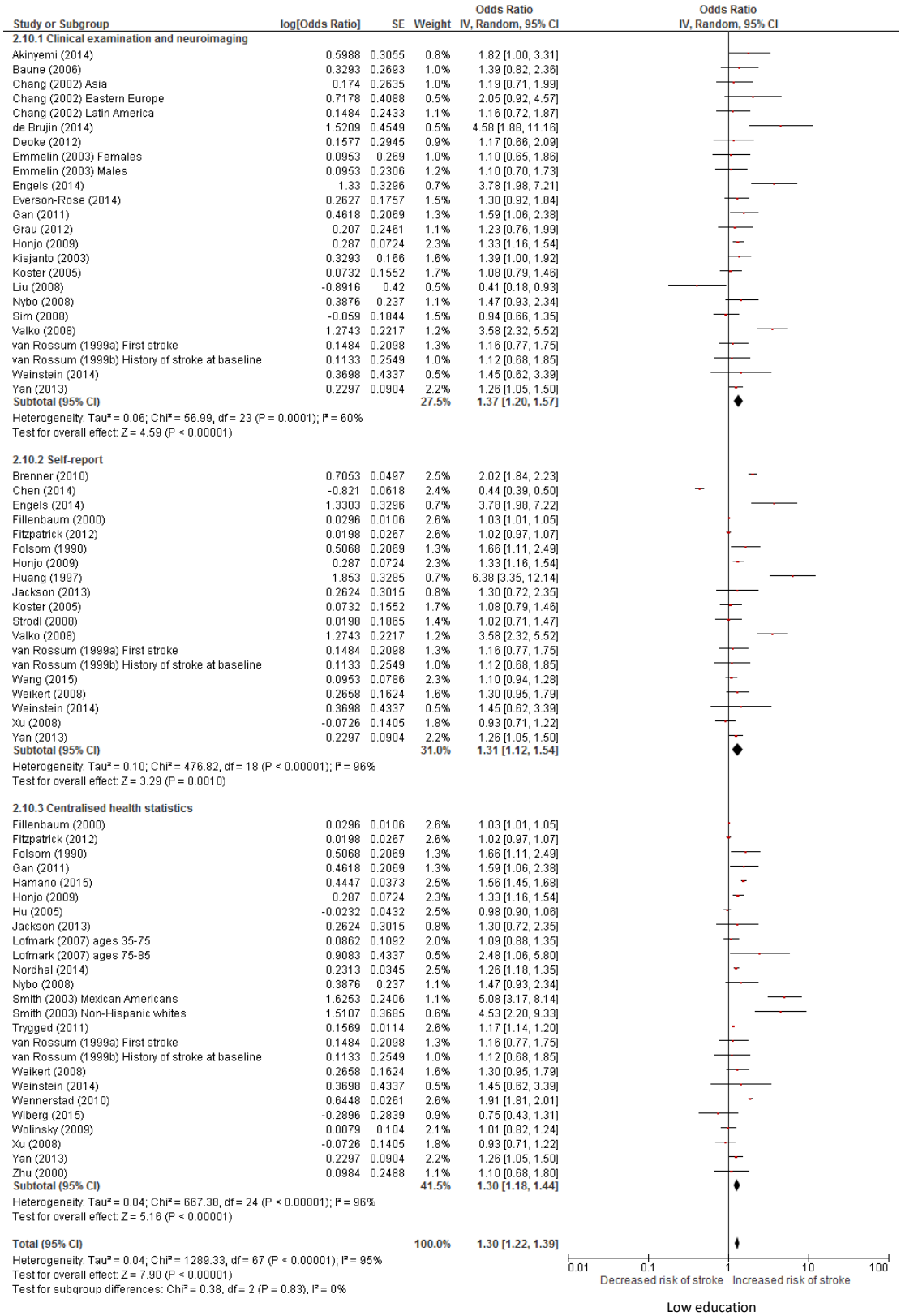
NOTE: Studies without footnotes report unadjusted results

Appendix 2I: Sensitivity analysis comparing population cohort studies vs hospital/outpatient studies by education level and risk of stroke; OR>1= low education increases risk of stroke.



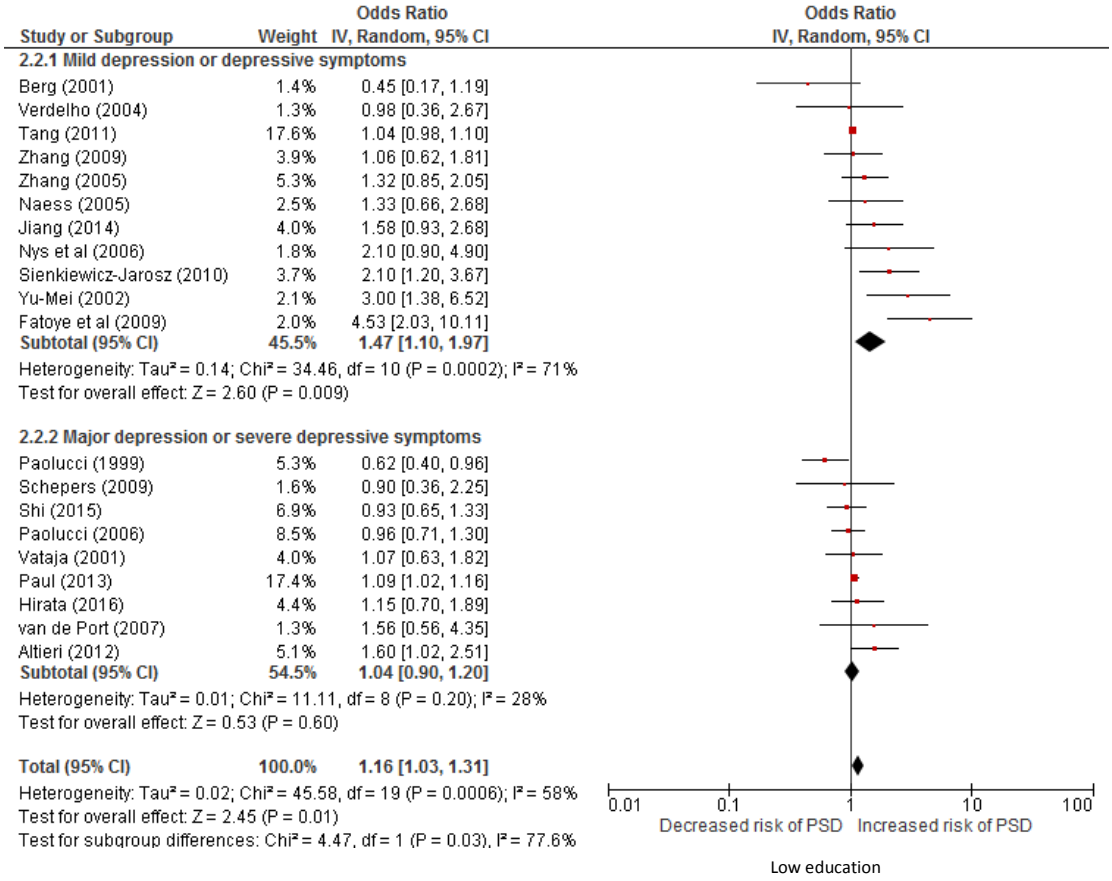
NOTE: Studies without footnotes report unadjusted results

Appendix 2J:. Sensitivity analysis comparing stroke ascertainment methods (clinical examination, self-report, central health statistics) by education level and risk of stroke; OR>1= low education increases risk of stroke



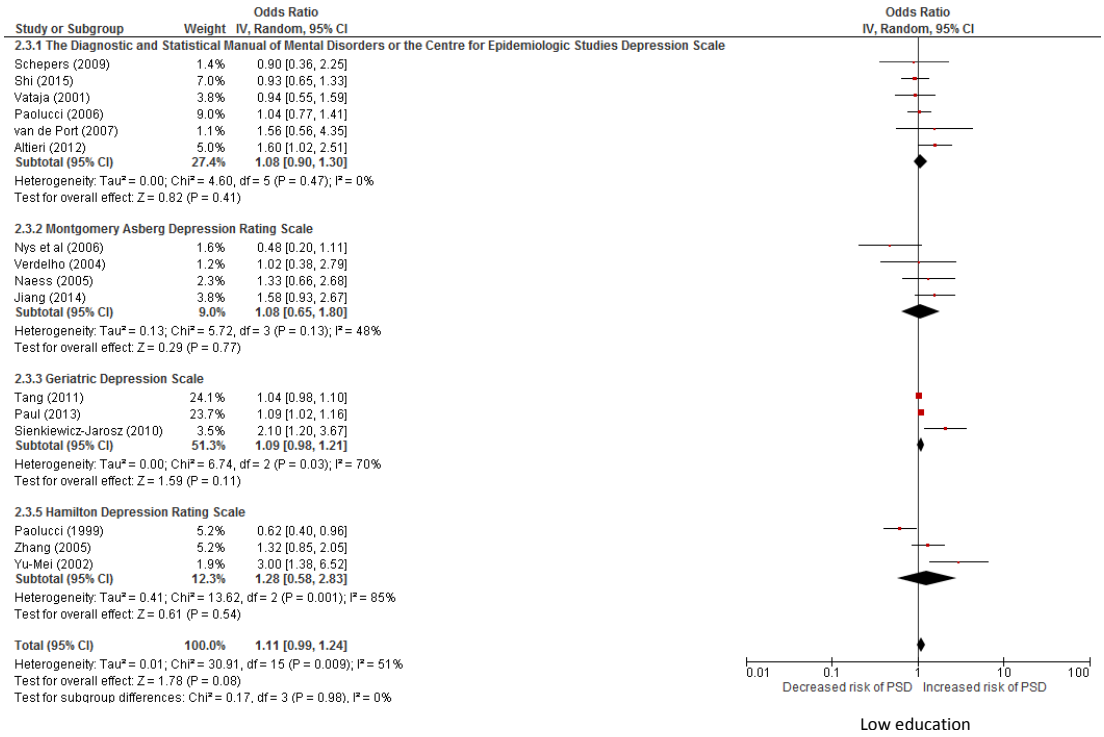
Appendices 2K-R: Sensitivity analysis for studies examining education level and post-stroke depression.

Appendix 2K: Sensitivity analysis comparing post-stroke depression measurement: Mild depression or depressive symptoms vs major depression or severe depressive symptoms by education level; OR>1=low education increases risk of post-stroke depression.



NOTE: Studies without footnotes report unadjusted results

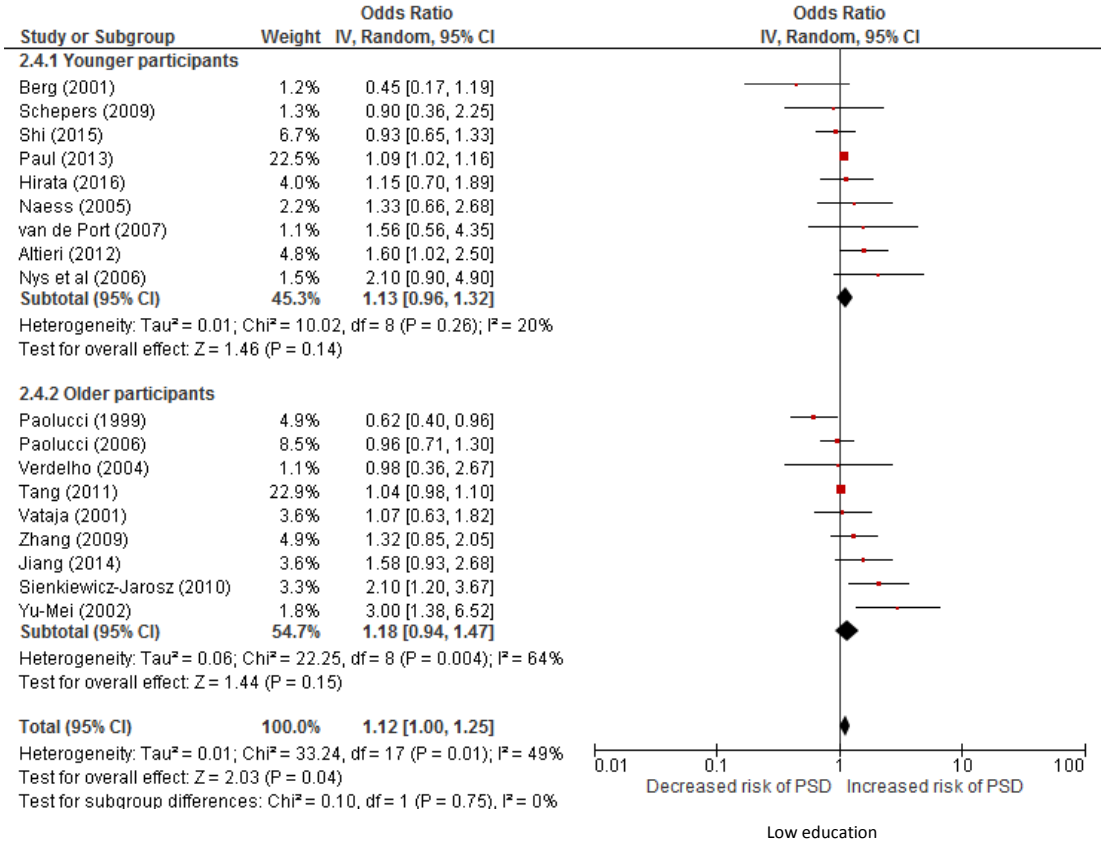
Appendix 2L: Sensitivity analysis comparing studies according to the depression scale used by education level and risk of post-stroke depression; OR>1=low education increases risk of post-stroke depression.



NOTE: Studies without footnotes report unadjusted results

Appendix 2M: Sensitivity analysis comparing studies that included younger (mean age <65 years) vs those that included older (mean age >=65 years) participants by

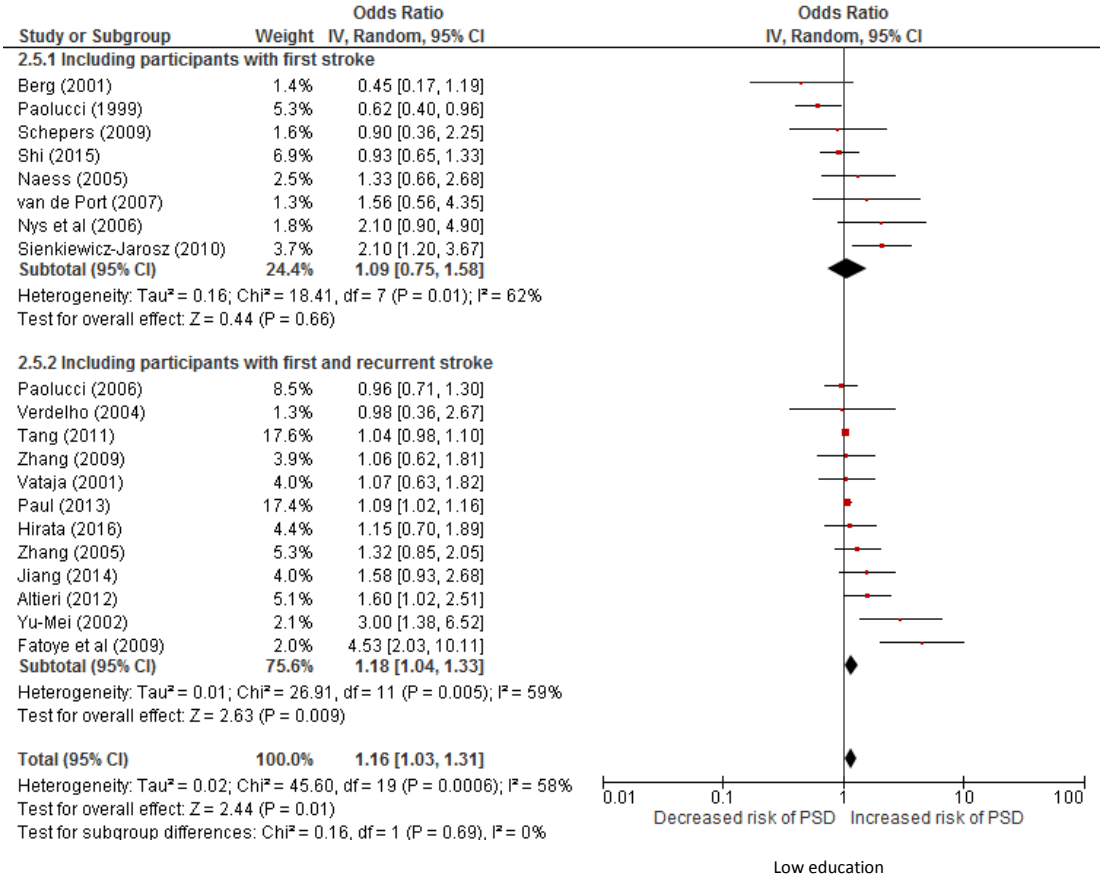
education level and risk of post-stroke depression; OR>1=low education increases risk of post-stroke depression.



NOTE: Studies without footnotes report unadjusted results

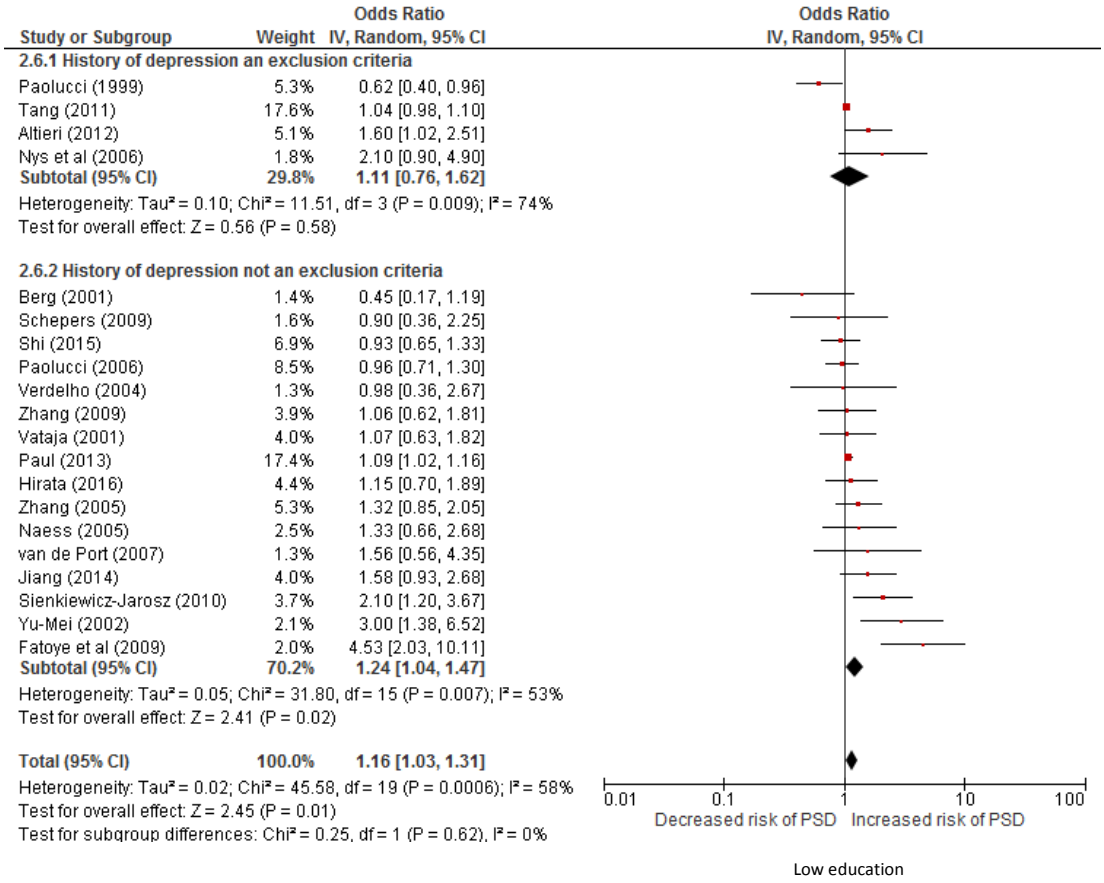
Appendix 2N: Sensitivity analysis comparing studies with participants with first stroke vs studies with participants with first and recurrent stroke by education level

and risk of post-stroke depression; OR>1=low education increases risk of post-stroke depression.



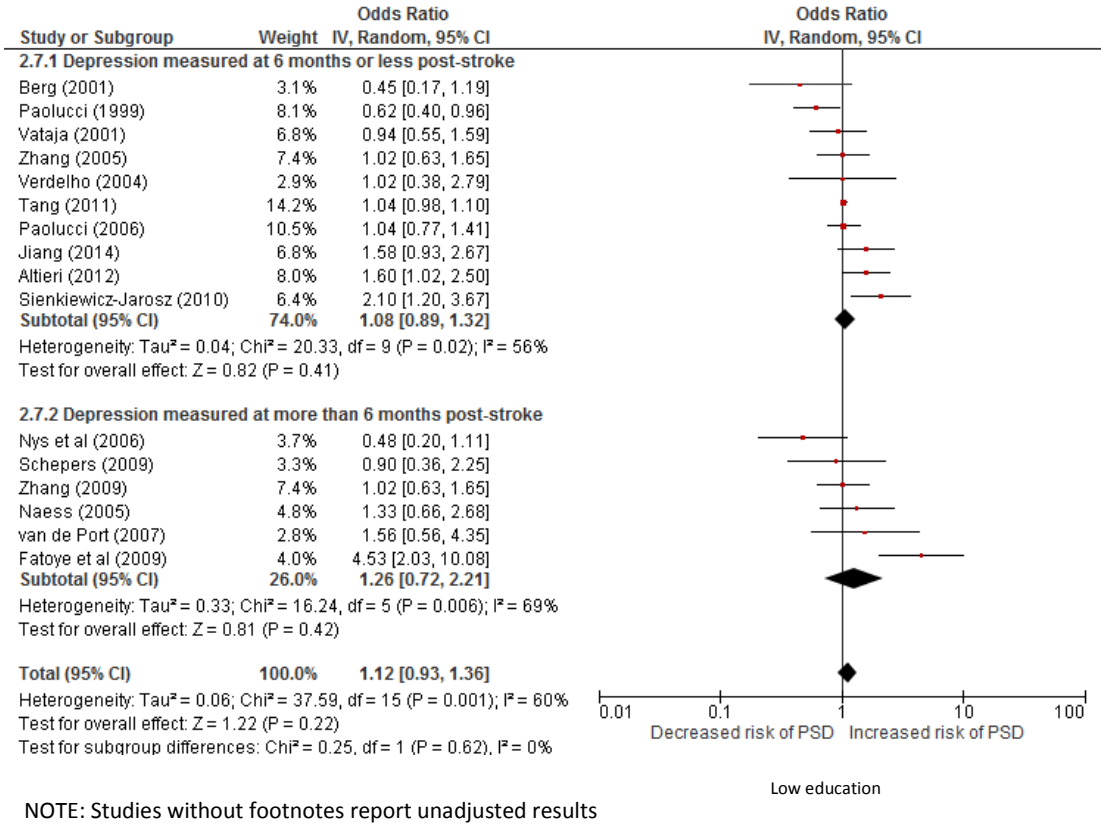
NOTE: Studies without footnotes report unadjusted results

Appendix 2O: Sensitivity analysis comparing studies with participants with depression as an exclusion criteria vs studies without depression as an exclusion criteria by education level and risk of post-stroke depression; OR>1=low education increases risk of post-stroke depression.



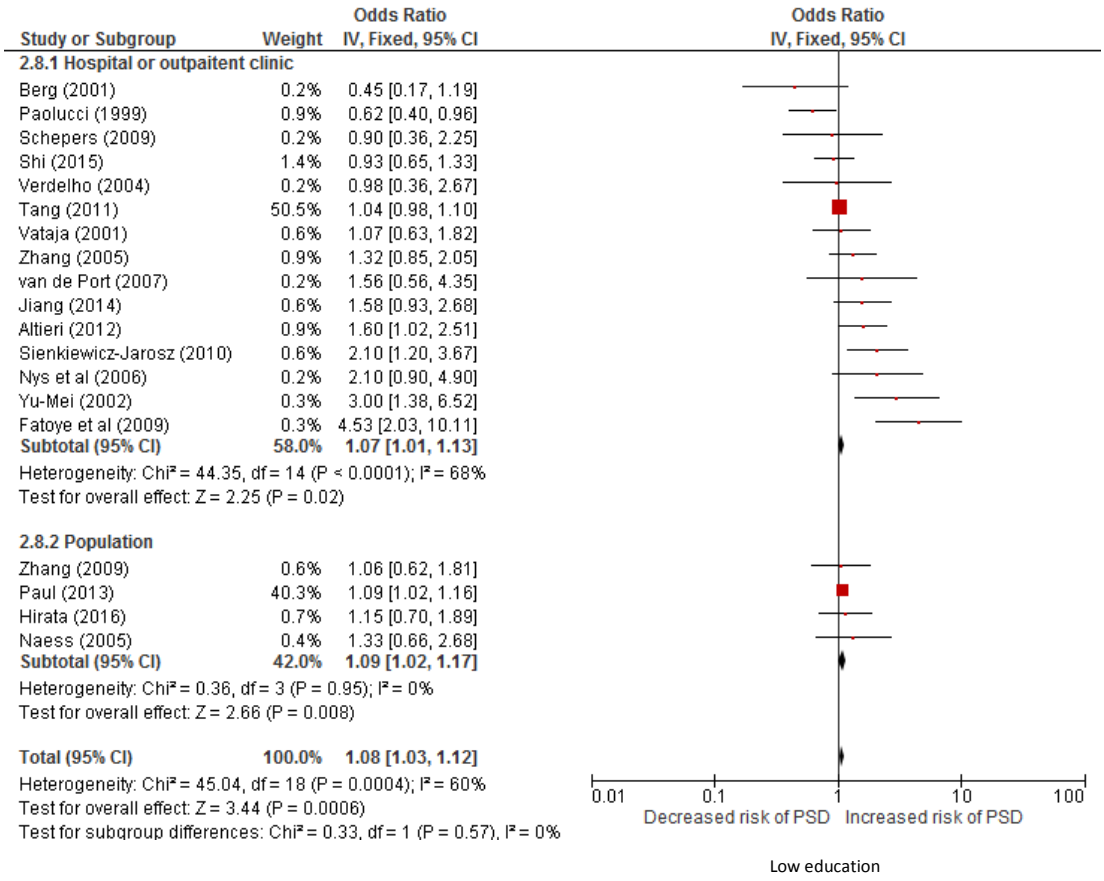
NOTE: Studies without footnotes report unadjusted results

Appendix 2P: Sensitivity analysis comparing studies with depression measured at 6 months or less vs studies with depression measured at more than 6 months post stroke by education level and risk of post-stroke depression; OR>1=low education increases risk of post-stroke depression.



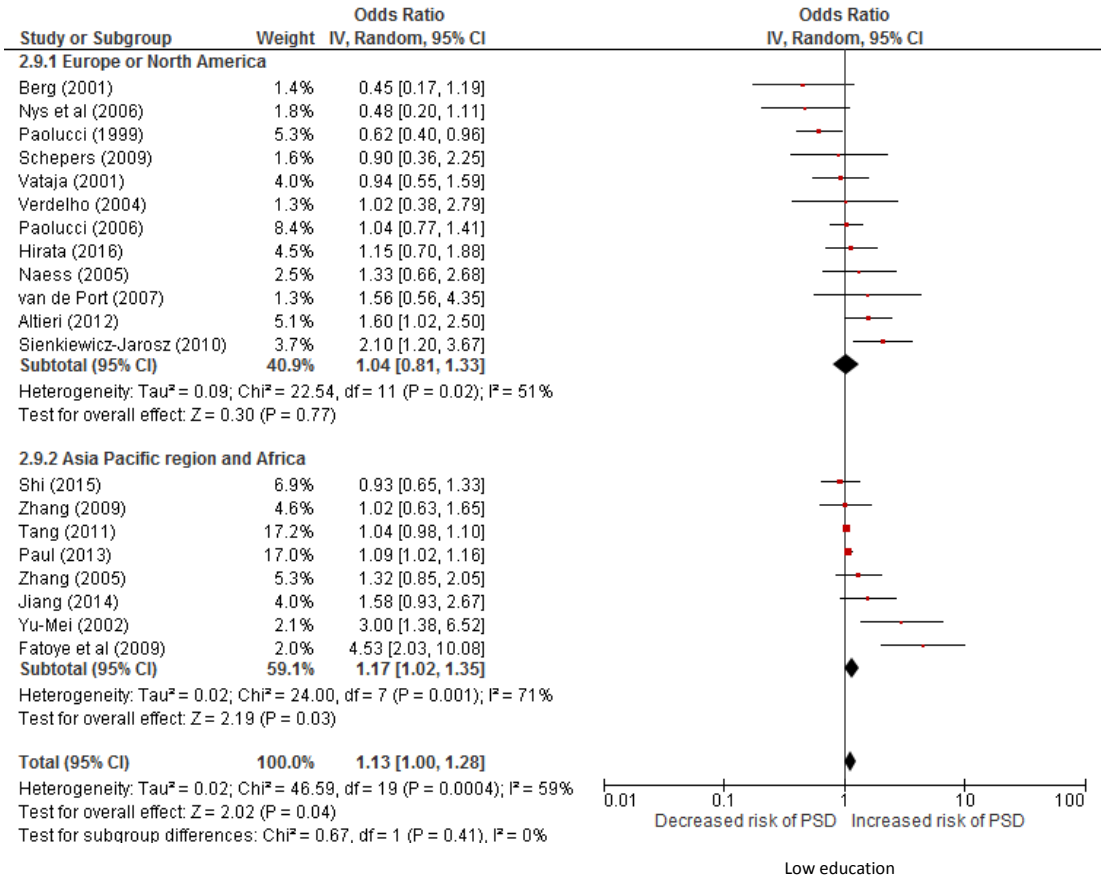
NOTE: Studies without footnotes report unadjusted results

Appendix 2Q: Sensitivity analysis comparing population cohort studies vs hospital/outpatient studies by education level and risk of post-stroke depression; OR>1=low education increases risk of post-stroke depression.



NOTE: Studies without footnotes report unadjusted results

Appendix 2R: Sensitivity analysis comparing studies conducted in Europe or North America vs the Asia Pacific region or Africa by education level and risk of PSD; OR>1=low education increases risk of stroke.



NOTE: Studies without footnotes report unadjusted results

Appendix 3A: Coding form used to read MRI scans in STRADL and the Dutch Famine Birth cohort.

MRI Grading Form STRADL 20160304

Patient Initials ..... Sex M / F Participant code .....

MRI date ...../...../..... Date coded ...../...../..... Reader .....

Date entered into database ...../...../..... Data entered by .....

Sequences (circle): T1 / T2 / FLAIR / GRE / DWI / SWAN / other.....

To be cross checked Y / N Cross check complete Y / N

Old infarcts: Y / N

	1	2	3	4	5	6	7	8
Left / Right	☐	☐	☐	☐	☐	☐	☐	☐
Code*	☐	☐	☐	☐	☐	☐	☐	☐
Infarct / Haemorrhage	☐	☐	☐	☐	☐	☐	☐	☐
If lacunar, cavitated Y**/N***	☐	☐	☐	☐	☐	☐	☐	☐

* Record in the following order: MCA cortical > other cortical > lacunar > cerebellum > brainstem
** Defined as a 'CSF-containing cavity' in an appropriate site, measuring 3-20mm in diameter
*** Defined as high signal on both T2 and FLAIR and of non-CSF signal on T1, and either (1) where no/minimal WMH: typical site, size & configuration (2) where moderate/severe WMH: typical site, size & configuration & very clearly distinct from WMH

Infarct codes – for acute/relevant or old, and for siderosis location

MCA cortical	***Other cortical***	***Lacunar****	***Cerebellum***
1 small cortical	*9 < half ACA*	*15 int & ext capsules/lent nucleus*	*22 small cortical*
2 basal ganglia	*10 > half ACA*	*16 internal border zone*	*23 <1/2 hemisphere*
3 subcortical	*11 < half PCA*	*17 centrum semiovale*	*24 >1/2 hemisphere*
*4 ant half periph MCA**	*12 > half PCA*	*18 thalamus*	
*5 post half periph MCA**	*13 anterior BZ*	*19 brainstem*	***Brainstem***
6 whole peripheral MCA	*14 posterior BZ*	*20 anterior (mainly) borderzone*	*25 small (i.e. <1/2 medulla)*
7 whole periph + lat BG		*21 posterior (mainly) borderzone*	*26 extensive (>1/2 medulla)*
8 whole MCA territory		*27 cerebellum*	
**note may include some of lateral basal ganglia*		*28 optic radiation*	

Total lacunes**

	L	R	Total
Lentiform	☐	☐	☐
Internal/external capsule	☐	☐	☐
thalamus	☐	☐	☐
centrum semiovale	☐	☐	☐
optic radiation	☐	☐	☐
cerebellum	☐	☐	☐

White matter hyperintensities

Fazekas *0 / 1 / 2 / 3*	L	R	Overall- use worst score
Periventricular	☐	☐	☐
Deep	☐	☐	☐

Wahlund *0 / 1 / 2 / 3*	L	R	Overall- add L+R scores
Frontal	☐	☐	☐
Parieto-occipital	☐	☐	☐
Temporal	☐	☐	☐
Infratentorial	☐	☐	☐
Basal ganglia	☐	☐	☐

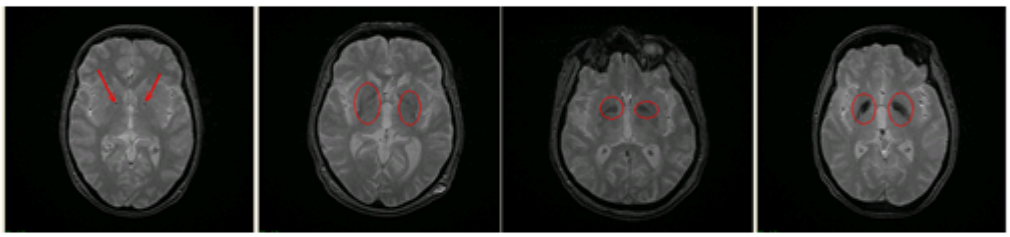
Enlarged perivascular spaces *0 = none / 1 = <10 / 2 = 11-20 / 3 = 21-40 / 4 = >40*

	L	R	Overall
Midbrain	☐	☐	☐
Hippocampus	☐	☐	☐
Basal ganglia	☐	☐	☐
Centrum semiovale	☐	☐	☐

Microbleeds: (indicate total number at each site) visible on:

	L	R	Overall	SWI/GRE/both
Grey/white matter junction	☐	☐	☐	☐
Deep white matter	☐	☐	☐	☐
Basal ganglia	☐	☐	☐	☐
Internal/external capsule	☐	☐	☐	☐
Thalamus	☐	☐	☐	☐
Posterior fossa	☐	☐	☐	☐

Basal Ganglia Iron deposits



none (1), minimal (2), some (3), much (4).

L: ☐ R: ☐

Is there any superficial siderosis*: Y/N_____ **If Y, is it focal or disseminated** F/D_____

If Y, give: **Side:** ☐ ☐ ☐ ☐ ☐

Location*: ☐ ☐ ☐ ☐ ☐

Is there any arterial ectasia? Y/N_____

If Y, tick all arteries affected: ICA: L_____ R_____

MCA: L_____ R_____

BA: _____

Atrophy (circle response; use normative age template)

Deep atrophy: _____ **1**(<25th)/ **2**(25-50th)/ **3** (50-75th)/ **4** (75-95th)/ **5** (>95th) / >>5 use **6**

Superficial atrophy: _____ **1**(<25th)/ **2**(25-50th)/ **3** (50-75th)/ **4** (75-95th)/ **5** (>95th) / >>5 use **6**

Other abnormalities / additional comments.....

.....

Appendix 3: Publications related to this Thesis

Backhouse, EV., McHutchison, CA., Cvoro, V., Shenkin, SD., Wardlaw, JM. (2015) Early life risk factors for stroke and cognitive impairment. *Curr Epidemiol Rep* 1-8

Backhouse, EV., McHutchison, CA., Cvoro, V., Shenkin, SD., Wardlaw, J.M.(2017) Early life risk factors for subclinical cerebrovascular disease: A systematic review and meta-analysis. *Neurology* 88(10) 608-618.

McHutchison, CA., **Backhouse, EV**., Cvoro, V., Shenkin, SD., Wardlaw, JM. (2017) Early life risk factors for stroke: A systematic review and meta-analysis. *Epidemiology* 28(4), 608-618

Backhouse, EV., McHutchison, CA., Cvoro, V., Shenkin, SD., Wardlaw, J.M.(2018) Cognitive ability, education and socioeconomic status in childhood and risk of post-stroke depression: a systematic review and meta-analysis. *PLoS ONE,* 13(7), e0200525.

Curr Epidemiol Rep
DOI 10.1007/s40471-015-0051-7

CARDIOVASCULAR DISEASE (LD LISABETH, SECTION EDITOR)

Early Life Risk Factors for Stroke and Cognitive Impairment

Ellen V. Backhouse[1] · Caroline A. McHutchison[1] · Vera Cvoro[1] · Susan D. Shenkin[2] · Joanna M. Wardlaw[1]

Abstract Cerebrovascular disease may present in later life with stroke or cognitive impairment and dementia, or may be silent, with changes seen incidentally on imaging or pathology. Midlife vascular risk factors such as hypertension, smoking and diabetes are well recognised. However, factors from much earlier in life may contribute to later vascular risk. In this commentary, we outline the importance of considering the whole life course in the development of cerebrovascular disease. We consider mainly factors from childhood, childhood intelligence test scores, education and socioeconomic status, which have been shown to contribute to stroke and cognitive impairment. Factors from even earlier in life, e.g. birth weight and breastfeeding also influence vascular risk factors. We discuss potential mechanisms for the observed relationships, e.g. whether childhood IQ or access to education may influence availability of social and economic resources and adoption of certain lifestyle choices and behaviours which are beneficial to health. Other possible mechanisms behind the observed relationships include differences in brain resilience and integrity reflected in intelligence which may lead to reduced susceptibility to cerebrovascular disease or the ability to sustain a higher degree of pathology before disease becomes clinically evident. Ongoing epidemiological, data linkage, imaging and translational studies are exploring the interrelationships and underlying mechanisms, but meanwhile, it is important to take a life course perspective when considering risk factors for cerebrovascular disease.

Keywords Stroke · Cerebrovascular disease · Cognition · Education · Childhood · Epidemiology

This article is part of the Topical Collection on *Cardiovascular Disease*

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Introduction

Cerebrovascular disease is common at older ages [1, 2] and results in ischemic and haemorrhagic stroke, transient ischemic attacks and cognitive impairment and dementia, gait and balance disorders and psychiatric symptoms [3]. Cerebrovascular disease also manifests as small vessel disease (SVD), which can present as clinically evident stroke, but more often is clinically 'silent' and if advanced causes dementia and physical disabilities [4]. SVD features are detected on imaging or at postmortem [4] as white matter hyperintensities (WMH), lacunes, micro-bleeds and other features [4, 5••].

Stroke is estimated to affect 1 in 20 adults in developed countries [2]. Subclinical cerebrovascular brain changes such as WMH and silent infarcts are found in 7 and 2 % of people aged 50–69, increasing to 17 and 7.5 % in those aged 70–89

[6]. Traditionally, midlife vascular risk factors such as hypertension, smoking and diabetes have been the main focus for risk factor studies and prevention trials for stroke, SVD and cognitive impairment. However, these variables do not fully explain the risk of later life disease. One study reported the cumulative incidence of clinical stroke to be 6.8 % in those with WMH and 1.4 % in those without [7]. It is unclear why some individuals can sustain a higher degree of neuropathological change before any clinical presentations occur. It is possible that there exist individual differences in the amount of brain damage or pathology that can be tolerated before reaching a threshold for clinical expression.

It is now recognised that a person's health trajectory is shaped by experiences across the lifetime (Fig. 1). The 'Barker hypothesis' now termed the 'Developmental Origins of Health and Disease' recognises that even before birth, intrauterine influences can result in permanent changes in physiology and metabolism which have a major impact on adult chronic health conditions, particularly coronary heart disease, hypertension and diabetes [8, 9]. These can be modified by later life experience; therefore, it is important to take a life course perspective when considering risk factors for cerebrovascular disease. Here, we outline the relationships between two main childhood factors—cognition and education—and later life stroke and associated cognitive impairment.

Lifelong Effects of Cognition on Cerebrovascular Disease

Childhood Cognition and Risk of Stroke

Childhood cognitive ability is associated with numerous health outcomes including longevity [10], general health [11] and several specific chronic health outcomes such as cardiovascular disease [12, 13], respiratory diseases [14] and stroke [12–16]. Furthermore, higher childhood intelligence is associated with better cognitive ability in older adulthood [17] and may influence later cognitive decline [18], perhaps by influencing peak adult cognitive function and/or the rate of cognitive decline [19].

Childhood intelligence has been identified as an important factor in determining the effect of age-related changes in the brain and development of overt cerebrovascular disease. Higher childhood IQ is associated with higher cognitive reserve, fewer WMH [20••] and better white matter integrity [21, 22]. For example, Shenkin and colleagues [22] found that scores on cognitive tests at age 11 and scores on the National Adult Reading Test (NART), a marker of premorbid cognitive function, correlated with diffusion tensor imaging parameters in the centrum semiovale at age 80. Pathological brain changes such as WMH have also been associated with childhood

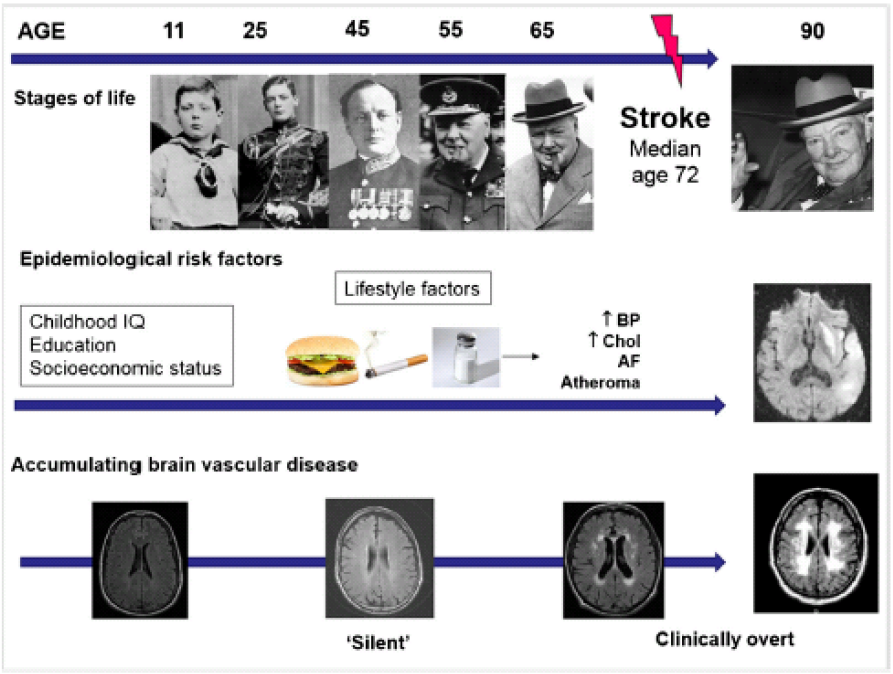

Fig. 1 The life course perspective of the risk of cerebrovascular disease and stroke

cognitive ability [20••]. A longitudinal study by Valdèz Hernàndez and colleagues [20••] reported an inverse relationship between age 11 IQ and WMH load around age 73. The strength of this relationship increased for those with evidence of previous clinical or subclinical stroke, with the volume of WMH almost doubled compared with those without stroke, independent of vascular risk factors.

How well does childhood cognitive ability predict later stroke? Some studies find that children with lower cognitive ability have a higher risk of stroke [12, 15, 23], although other studies found no such association after controlling for other risk factors [13, 16]. This is perhaps due to the difficulty of classifying stroke retrospectively and without imaging or lack of availability of information regarding childhood cognitive scores. However, the NART [24], The Mill Hill and the Wechsler Test of Adult Reading (WTAR) [25] which assess crystallised intelligence can be used to measure premorbid IQ. These measures are built on the assumption that reading ability, an aspect of crystallised intelligence, remains constant regardless of age or damage to the brain [26] and scores in old age have been shown to correlate highly with childhood IQ [27]. Furthermore, poor performance on tests of crystallised intelligence has been associated with cognitive impairment following stroke [28].

Interpretation of these studies may be difficult due to differing study designs, populations and measurements. Additional residual confounding by other factors that may affect childhood IQ and stroke must also be considered. These factors include genetics [29], early life social, environmental and nutritional factors [30, 31•, 32], education [23] and socioeconomic status (SES) [15]. It is important to consider all of these and how they relate to one another across the life course when considering risk of disease.

Education and Risk of Stroke

Several small studies have demonstrated the relationship between education and neuropathological changes associated with cerebrovascular disease [33, 34•]. For example, people with lower levels of education have a higher frequency of cerebrovascular lesions and SVD [34•] including infarcts, lacunes and white matter rarefaction [33]. However, it is unclear whether these studies adjusted for health-related behaviours such as smoking and alcohol use. This is an important factor to consider when interpreting results from such studies especially given the complex interrelationships between risk factors for cerebrovascular disease.

Education is inversely associated with risk of stroke [23]. Lawlor [23] reported that for every additional category of education, females were 41 % and males were 16 % less likely to have a stroke. After adjustment for other early life factors such as IQ, this decreased slightly to 35 and 10 % for females and males, respectively.

Education has been associated with events following stroke such as cognitive impairment [35] and mortality [31•, 35]. Long educational history has been associated with lower frequency of cognitive deficits and improved long-term survival in patients following stroke after adjustment for age, WMH and stroke severity [35]. Another larger study of stroke patients from across Sweden [31•] reported that university education was independently and positively associated with survival following the first ever stroke. This relationship was consistent across gender, age and time period after stroke and independent of stroke severity.

Educational attainment is strongly related to both cognitive ability and SES [36] which in itself has been associated with cerebrovascular disease risk. A systematic review of nine studies reported a strong relationship between childhood socioeconomic circumstances and risk of stroke in later life [37]. The association between education and SES means that education is often used as an indicator of SES; however, their relationship may be bidirectional, for example, unfavourable socioeconomic circumstances can restrict opportunities for or access to higher education.

The Relationship Between Education and Childhood IQ

Childhood IQ and educational attainment are closely linked [38], and several researchers have suggested that education may be a surrogate for cognitive ability. IQ may influence educational choices with more intelligent people accessing higher or further education. Higher IQ may also lead to more educational success [38], better employment opportunities and access to other socioeconomic benefits associated with achieving better health. Adjustment for education [12, 16] and other socioeconomic factors [16, 23] in the intelligence-health relation has largely shown a consistent and strong attenuating effect. Conversely, controlling for intelligence in the education-health (including stroke) relationship had little effect [39].

Individuals with contrasting levels of education and IQ may provide a unique opportunity to separately assess these variables in relation to health. Link and colleagues [39] reported that positive health outcomes were more strongly predicted by higher levels of education than higher levels of intelligence. This suggests that education may have a positive effect on improving health outcomes regardless of IQ.

However, the relationship between these variables is complex. It is plausible that education may represent at least a partial proxy to childhood cognitive ability, as variance in educational outcome is to a substantial extent a reflection of differences in mental ability. However, it can also be argued that education exerts at least a small amount of influence on health independent of the effect of childhood mental ability [39] as indicated by the apparent protective effect of exposure to minimal amount of schooling on cerebrovascular disease risk [34•].

Cognitive Decline Prior to Stroke

The interrelationships between lifetime cognition and stroke are complex. Cognitive impairment may be a very early and subtle indication of cerebrovascular disease [40]. Impaired cognition predicts later stroke risk, e.g. impaired executive function is associated with higher 10 year stroke risk [40]. Furthermore, impaired cognitive function in the few years before stroke can predict the onset of the first stroke better than conventional vascular risk factors, particularly in those over 85 years of age [41•]. A score of less than 24 on the Mini Mental State Exam (MMSE) was associated with a 35 % relative increase in stroke, comparable to the risk associated with a prior stroke [42]. A possible explanation for this is that cognitive impairment is an indication of subclinical vascular disease which may later result in stroke [43]. Consequently, selective cognitive tests may be a promising and sensitive screening tool for those most at risk of stroke or SVD but this requires validation. However, it is difficult to rule out reverse causation as it is tenable that unidentified risk factors or undiagnosed early cerebrovascular disease may be responsible for cognitive decline. One way to eliminate reverse causation is to measure risk factors in childhood, before development of midlife illness such as hypertension and diabetes which can also reduce cognitive ability [44, 45]. Longitudinal studies will also allow consideration of the possibility that impaired cognition is due to lifelong poorer cognitive function, rather than new cognitive impairment.

Cognition Following Stroke

Both clinical stroke and SVD are associated with an increased incidence of cognitive impairment and dementia [46]. Vascular cognitive impairment is defined by evidence of cerebrovascular disease as well as impairment in at least one cognitive domain assessed using validated measures [47–49]. Vascular dementia (VaD) is the second most common form of dementia after Alzheimer's disease and both may increase with the growing ageing population [50]. A diagnosis of VaD will be made when two or more cognitive domains are affected, associated with functional impairment [51]. The degree of impairment is determined by risk factors including increasing age [52], previous or recurrent strokes, WMH, hypertension, smoking, diabetes and atrial fibrillation [53]. However, as with risk of stroke, these conventional risk factors do not fully explain individual differences in occurrence of VaD or cognitive impairment.

In a systematic review of 30 patient cohorts ($n=7511$), the prevalence of post-stroke dementia varied from 7 to 40 % [53]. This variance may be in part due to whether the first ever or recurrent stroke was considered and also whether those with pre-stroke dementia were included. Pre-stoke dementia affects between 9 and 14 % of stroke patients, and those studies which excluded patients who had dementia before the stroke reported much lower prevalence than those who included such patients [53]. This provides support that a proportion of those who develop cognitive decline following stroke have some form of cognitive impairment before, and the stroke itself may trigger a decline in cognitive function. It is becoming increasingly recognised that it is important to consider pre-stroke cognitive impairment/dementia in the years leading up to stroke as it may affect cognition following stroke. However, as people often present suddenly with stroke, it can be difficult to measure pre-morbid cognition. Studies are using measures such as The Informant Questionnaire on Cognitive Decline in the Elderly [54] (IQ-CODE) to account for this. However, this measure can also be difficult to administer as it requires an informant to be available. The use of such measures will help to (a) control the assessment of post-stroke cognitive impairment for undiagnosed pre-stroke cognitive impairment and (b) help to address the recent observation that declining cognition in later life is itself a risk factor for stroke [42]. In other words, cognitive decline may lead to stroke and stroke leads to cognitive decline, in later life—the extent to which both are influenced by early life exposures, and whether these act synergistically on the risk of stroke and of cognitive decline in later life, remain to be determined.

Mechanisms Behind Observations

Several reasons have been proposed for the associations between early life factors and cerebrovascular disease and subsequent cognitive impairment.

(1.) *Behaviour and lifestyle*

Across the lifespan, the influence of behaviour and lifestyle on later life disease begins with genetic and parental exposures prior to birth. The socioeconomic status of an individual's parents can influence their exposure to risk factors for cerebrovascular disease and stroke both prior to birth and throughout childhood [55••]. These risk factors include poor nutrition, low birth weight [9], exposure to smoking [56] and decreased access to healthcare and education [39]. These factors in turn can influence childhood cognitive ability and level of education achieved. Education can shape access to social and economic resources and exposure to environments and occupations that may protect against certain health problems [39]. Similarly, intelligence can influence self-management of health and health-related information either as a preventative strategy or to address an existing problem [57]. Furthermore, intelligence may influence adoption of certain behaviours that are conducive to health such as level of

exercise, diet and alcohol consumption which influence risk of cerebrovascular disease. This is illustrated in the observation that individuals with higher childhood IQ are less likely to smoke in adulthood [58] and more likely to stop smoking by the age of 30 [11]. Higher risk of stroke, as measured by the Framingham stroke risk profile, predicts cognitive decline in multiple domains from midlife [59].

(2.) *Brain Integrity and Cognitive Reserve*

In addition to influencing behaviour and lifestyle, there is accumulating evidence that education and early life IQ act as a marker of neural integrity and some evidence that poor integrity of cerebral white matter may predict vulnerability to stroke and cognitive decline.

General cognitive ability is a lifelong, stable trait and therefore factors that determine or contribute to this are likely to begin in childhood. These overlapping factors may help explain the association between childhood intelligence and accumulation of silent cerebrovascular disease, e.g. white matter changes and vulnerability to stroke and cognitive impairment [60]. Cognitive information processing speed has long been recognised as a correlate of general intelligence and indicative of cognitive decline [61], and efficient information processing is thought to rely on the integrity of interconnecting white matter tracts [60]. For example, information processing speed has been shown to mediate the relationship between white matter tract integrity and general intelligence in the seventh decade [62].

White matter tract integrity can be measured using magnetic resonance diffusion tensor imaging (DTI) and can be used to assess white matter damage as a result of ageing or disease [63]. It provides two quantitative parameters, the mean diffusivity (< *D* >) and fractional anisotrophy (FA) which are used to indicate the amount of tissue damage evident in an individual. Fractional anistrophy has been shown to fall linearly with age, particularly in the frontal regions [64]. Cortical disconnection of these tracts can cause disruption of neurocognitive networks, and this has been proposed as a possible mechanism for the cognitive changes which underpin cognitive ageing [64].

Both education [65] and cognitive ability [21] have been associated with white matter integrity. Education has been found to be the main predictor of fibre tract integrity in several brain areas with those with higher levels of education having more richly connected fibre tracts [65]; however, this was not corrected for prior IQ. Longitudinal studies have reported that white matter integrity in the centrum semiovale at age 83 correlates with age 11 IQ and white matter integrity along with processing speed accounted for 85 % of age 83 general cognitive ability [21]. What is less certain is the degree to which lifetime brain integrity protects against cerebrovascular disease in later life and whether any such association can be influenced by exposure to more or less education.

Early life factors may influence the development of stroke and cognitive impairment through their effect on cerebrovascular disease markers such as WMH [20••, 34•, 66]. Education and cognitive ability may provide a protective advantage in two ways; firstly, they may provide resilience against the development of white matter changes as shown by the inverse relationship between WMH and age 11 IQ [20••]. Secondly, early life factors may provide resilience to the effects of WMH by increasing the threshold of pathological load required in order to develop clinically evident disease, perhaps by reducing the impact of cerebrovascular pathology on cognition [34•, 66]. Education may modify the relationship between white matter changes and cognition [34•, 66]. Among those with low levels of education, the presence of WMH [66] or lacunar infarcts [34•] are associated with lower cognition. However, for those with more years of education, the likelihood of cognitive impairment from WMH and lacunar infarcts has been shown to be much lower [34•, 66]. These mechanisms are often referred to as the theory of cognitive reserve which proposes that greater brain integrity can protect the brain from negative neurological sequela through both 'active' and 'passive' pathways [67]. While passive cognitive reserve relates to histology and brain size, active reserve refers to the ability of redundant pathways to take over following damage to the brain [67].

Implications

Stroke and dementia are common, serious health conditions which have substantial cost implications for the national economies and cause a significant amount of distress and disability to patients and carers. Research into early life risk factors for cerebrovascular disease may help inform future interventions and planning of health and educational services and social policy to target those most at risk. Identifying risk and resilience factors in childhood will help highlight the lifelong level of vulnerability and guide development of prevention strategies that could be implemented from early childhood onwards.

Conclusion

Stroke increases the risk of, and is a major cause of, cognitive impairment or dementia; cognitive decline increases risk of stroke and is associated with 'silent' cerebrovascular disease features. Early life factors such as better childhood cognitive ability and education may protect against later risk of cerebrovascular disease and dementia, although the association may

be confounded by other genetic or environmental factors. Childhood cognitive ability and education may influence health behaviours and access to socioeconomic resources beneficial to health. Additionally, they may increase brain integrity and resilience leading to reduced susceptibility to cerebrovascular disease or to the ability to withstand higher pathologic load or moderate the relationship between SVD and clinical expression of disease. Education and cognitive ability are closely associated and education may be at least a partial proxy for IQ. Planned studies of clinical and population cohorts will help to understand these interrelationships and underlying mechanisms. This could then lead to the potential for exploring whether the risk factors early in life might be modifiable. Interventions to affect early life education or to preserve later life cognition are complex and may require changes in social policy or public health strategy. However, many strategies that could have a positive impact on cerebrovascular disease are those that would be priorities for government policy for other reasons. It is essential that the whole life course is included when considering risk factors for the development of stroke and post-stroke cognitive impairment.

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Compliance with Ethics Guidelines

Conflict of Interest EV Backhouse, CA McHutchison, V Cvoro, and SD Shenkin declare that they have no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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Early life risk factors for cerebrovascular disease

A systematic review and meta-analysis

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ABSTRACT

Objective: Cerebrovascular disease (CVD) causes subclinical brain vascular lesions detected using neuroimaging and childhood factors may increase later CVD risk.

Methods: We searched MEDLINE, PsycINFO, and EMBASE, and meta-analyzed all available evidence on childhood (premorbid) IQ, socioeconomic status (SES), education, and subclinical CVD in later life. Overall odds ratios (OR), mean difference or correlation, and 95% confidence intervals (CIs) were calculated using random effects methods.

Results: We identified 30 relevant studies (n = 22,890). Lower childhood IQ and lower childhood SES were associated with more white matter hyperintensities (WMH) (IQ: n = 1,512, $r = -0.07$, 95% CI −0.12 to −0.02, $p = 0.007$; SES: n = 243, deep WMH $r = -0.18$, periventricular WMH $r = -0.146$). Fewer years of education were associated with several CVD markers (n = 15,439, OR = 1.17, 95% CI 1.05 to 1.31, $p = 0.003$). No studies assessed early life factors combined.

Conclusions: Childhood IQ, SES, and education are associated with increased risk of CVD on neuroimaging in later life. Further studies are required to provide further evidence and thereby inform policy. *Neurology*® 2017;88:976–984

GLOSSARY

CI = confidence interval; **CVD** = cerebrovascular disease; **MD** = mean difference; **OR** = odds ratio; **SES** = socioeconomic status; **SVD** = small vessel disease; **WMH** = white matter hyperintensities.

Cerebrovascular disease (CVD) is common at older ages,[1,2] causing stroke, TIA, and dementia.[3] Cerebral small vessel disease (SVD), a common feature of CVD, affects small penetrating brain blood vessels, damaging the white and deep gray matter. This can result in clinical stroke but also subclinical brain changes[3] that are detected on neuroimaging or postmortem[3] including white matter hyperintensities (WMH), lacunes, microbleeds, and small infarcts.[3,4] While WMH are recognized increasingly to reflect complex pathologies, they generally reflect vascular malfunction and therefore indicate CVD/SVD. SVD is the commonest vascular cause of dementia,[2] causes one-fifth of strokes,[5] and is associated with cognitive, psychiatric, and physical disabilities.[3,6]

Midlife vascular risk factors for SVD such as hypertension, diabetes, and several lifestyle factors are well-established. However, individual studies suggest that factors earlier in life, including childhood cognitive ability,[7,8] education,[9,10] and socioeconomic status (SES),[11] may also contribute to CVD in later life. The extent to which this applies across all studies and all 3 predictors (cognitive ability, SES, and education) is not known.

Following an initial scoping of the literature,[12] the current systematic review and meta-analysis aimed to assess relationships among intelligence (IQ), SES, and education in youth and risk of subclinical cerebrovascular disease (i.e., on neuroimaging or pathology) in later life.

METHODS We used PRISMA and MOOSE guidelines,[13] and registered the protocol prospectively on Prospero (registration number: CRD42015016701).

Search methods. We developed and tested a detailed search strategy (supplemental material e-1 at Neurology.org) to identify studies examining education, childhood intelligence/premorbid IQ, or childhood SES and cerebrovascular disease including clinically overt (i.e.,

Supplemental data at Neurology.org

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stroke,[14] cognitive impairment, depression) or silent (subclinical) cerebrovascular disease detected on neuroimaging or pathology. Here we report on subclinical cerebrovascular disease.

We searched PsycINFO, MEDLINE, and EMBASE from inception for articles published until November 30, 2015, using OVID SP UI03.16.00.110. We checked reference lists of included articles and review articles and hand-searched the previous 5 years of *Stroke*, *Neurology*®, and *International Journal of Epidemiology*.

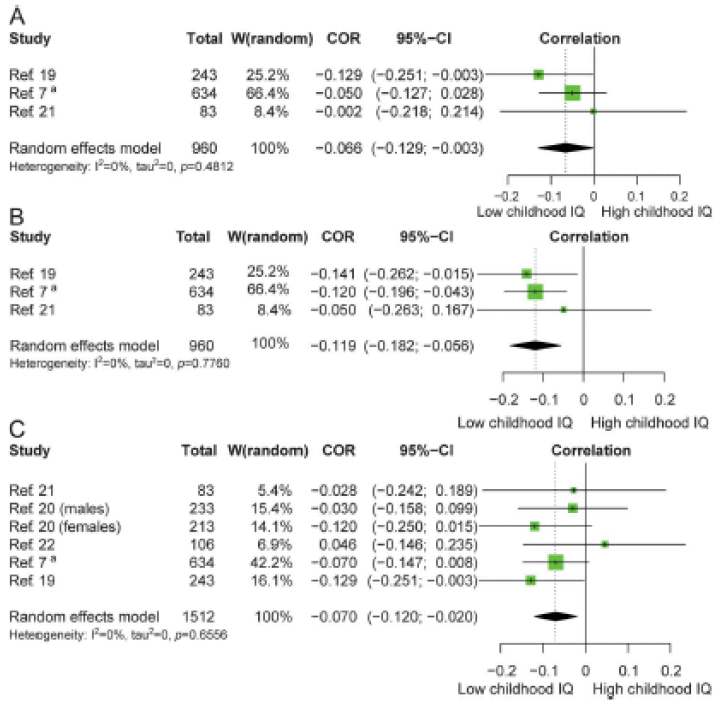
Abstracts and titles were screened by 1 reviewer and full texts were screened independently by 2 researchers. Disagreements were resolved through discussion among the authors. Data from publications on the same cohort were taken from the most recent publication or the one with the largest sample. Eligible articles were grouped according to early life factor.

Inclusion criteria. Studies were included if they provided data on early life factors in relation to neuroimaging or pathology evidence of CVD in adulthood. We included general intelligence (IQ) measurements performed up to age 18 years and estimates of premorbid IQ using valid tools (e.g., Spot-The-Word Test). We included childhood SES measures such as parental occupation. All measures of childhood education were included (duration, attainment). We defined subclinical CVD as WMH, lacunes, silent infarcts, or microbleeds according to the Standards for Reporting Vascular Changes on Neuroimaging[4] if on MRI or CT, or the equivalent features if on pathology. We noted WMH quantification method, e.g., visual scale (Fazekas or other) or volume. The Fazekas scale[15] rates WMH in the periventricular and subcortical region (0–3 scale). The Scheltens scale[16] additionally scores hyperintensities in the basal ganglia and infratentorial region (0–24 scale). These regions can be reported separately or summed to give a total score. We meta-analyzed correlation coefficients for IQ and periventricular WMH, deep WMH, and total WMH burden (figure 1). We excluded articles with fewer than 50 patients and those focusing on a particular patient population (e.g., Parkinson disease), without primary data, published only in abstract, or not reporting neuroimaging data on humans aged 18 or over. We considered articles in any language.

Data extraction and quality assessment. One reviewer (E.V.B. or C.A.M.) extracted data and cross-checked each extraction form; J.M.W., S.D.S., and V.C. cross-checked a sample. We extracted data on study and participant characteristics, definition and measurement of early life factor, outcome, and statistics, including whether the effect size was adjusted for vascular or other risk factors, or crude.

We assessed methodologic quality for 6 potential sources of bias[17]: representativeness of the sample, attrition, how early life factor and outcome were measured, adjustment for confounders,

Figure 1 Forest plots showing correlation (COR) between childhood IQ and (A) deep white matter hyperintensity (WMH) burden, (B) periventricular hyperintensity burden, and (C) total WMH burden



Lower childhood IQ was associated with higher WMH burden in late life. CI = confidence interval. [a] Adjusted for age, sex, and hypertension.

Table 1 Studies included in systematic review of early life factors and subclinical cerebrovascular disease

	Childhood IQ	Childhood SES	Education
No. of articles identified	8	1	30
No. of studies included	5	1	26
Study setting			
Population	4	1	16
Hospital	0	0	1
Community	1	0	6
Outpatient clinic	0	0	5
Autopsy	0	0	1
Total no. of participants	1,512	243	22,357
Age range of included studies, y	60-78.3	68	45-85.2
Outcome			
WMH	5	1	16
Microbleeds	0	0	4
Lacunes	0	0	2
Infarcts	0	0	4
SVD	0	0	6
Quality score[a]	21 (1)	21	21 (2)
Range	17-22	21	17-24

Abbreviations: SES = socioeconomic status; SVD = small vessel disease; WMH = white matter hyperintensities.
Some studies fall into multiple categories.
[a] Median (interquartile range).

and appropriateness of the statistics. We scored each item between 1 and 4 (corresponding to unclear, no, partly, yes), giving a total score of 24, with higher scores indicating better quality.

Statistical analysis. Within each early life factor, we grouped articles according to reported outcome statistic (e.g., odds ratio [OR], mean values). Where multiple statistics were reported, we used the one that maximized data available for meta-analysis. Markers of CVD were analyzed together to produce an overall result, and separately in prespecified subgroup analysis.

One article reported childhood SES using parental occupation classed as manual and nonmanual representing low and high childhood SES, respectively. We standardized all education results to represent a reference level of high education. With the exception of one study,[9] low education was defined as approximately 6–8 years (less than high school) and high education as 9 years and over (high school and above).

We used Review Manager v5.3 to calculate overall ORs or mean differences (MD) and 95% confidence intervals (CIs). We analyzed correlation coefficients using the package metacor for R v3.0.1. Where possible, we used risk factor–adjusted results. Where necessary, we calculated ORs from frequency data. We analyzed articles that reported means or medians separately. Medians were included in the MD analysis as medians. We used a random effects model in anticipation of between-study heterogeneity and assessed heterogeneity using the I^2 statistic. We assessed publication bias with funnel plots.

RESULTS We identified 19,180 titles and abstracts after removal of duplicates (figure e-1), from which we identified 1,217 full-text articles. The commonest reason for exclusion was lack of an appropriate outcome. Thirty articles that examined early life factors and subclinical CVD met inclusion criteria (table 1, full details in table e-1). Most studies assessed CVD with neuroimaging; 2 population studies assessed CVD postmortem.[9,18]

Quality assessment and publication bias. Quality scores ranged from 17 to 24/24. Most articles were scored as "good" (3/4) on statistics and measurement of early life factor but less well on confounding factors (figure e-2).

It was not possible to determine publication bias for all analyses due to few studies for some comparisons. However, in analyses with several studies, there was no good evidence of publication bias (figure e-3).

Childhood IQ. Five studies,[7,19–22] reported in 8 articles, examined childhood IQ and subclinical CVD, including 1,512 participants aged 60–78 years at MRI. All studies assessed WMH only (Fazekas or Scheltens scale), and reported results as correlations. Most studies used IQ obtained at age 11 (4 articles[7,19,21,22]) while one[20] estimated premorbid IQ in adulthood (Spot-the-Word test).

Overall, lower childhood IQ was associated with increased deep WMH scores ($r = -0.066$, 95% CI −0.129 to −0.003, $p = 0.04$, figure 1A), periventricular WMH scores ($r = -0.12$, 95% CI −0.182 to −0.056, $p \leq 0.001$, figure 1B), and total WMH scores ($r = -0.07$, 95% CI −0.12 to −0.02, $p = 0.007$, figure 1C). One study[7] provided risk factor–adjusted results. Heterogeneity between studies was low (I^2 0%, $p = 0.66$).

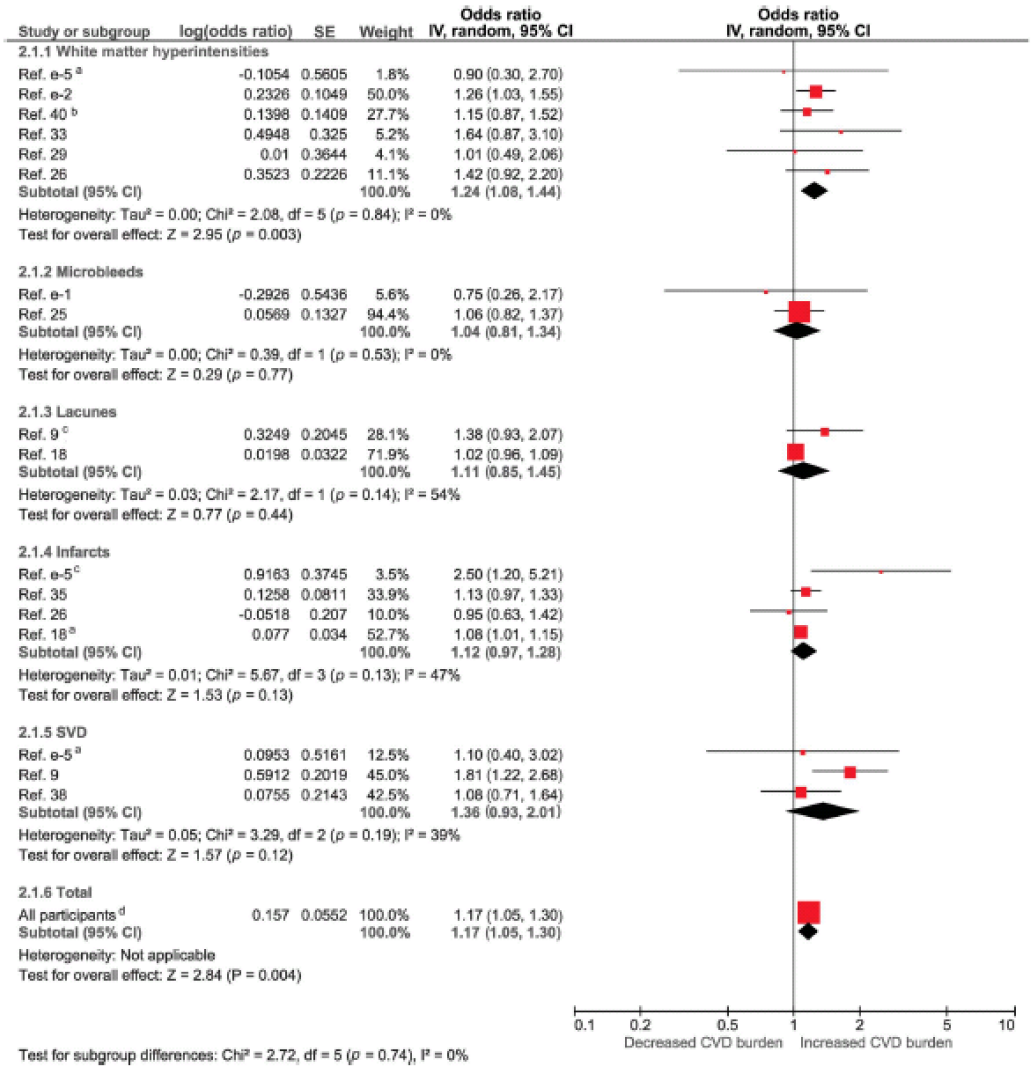
Childhood SES. One study[19] (n = 243) found that lower childhood SES (measured as father's manual vs office-based occupation, 6 categories, lower score indicating manual occupation, more childhood deprivation) correlated with more deep WMH ($r = -0.181$, $p < 0.05$) and periventricular WMH ($r = -0.146$, $p \leq 0.001$) at age 68.

Education. Twenty-six studies[9,18,19,23–40,e1–5] reported in 30 publications examined education and subclinical CVD, including 22,357 participants aged 45–84 years at MRI. The most common markers of subclinical CVD were WMH (16 studies[19,23,24,26,27,29–36,40,e2,e5]), microbleeds (4 studies[25,30,e1,e5]), infarcts (4 studies[18,26,35,e5]), and lacunes (2 studies[9,18]), and 6 studies[9,28,37,38,e4,e5] examined combined markers of SVD.

Education level was assessed as duration (i.e., <8 years vs ≥8 years) in 7 studies[18,26,30,31,38,40,e5] and attainment (i.e., primary vs secondary school) in 12 studies.[9,19,23–25,29,33,35,36,e1,e2,e4] Seven studies[27,28,32,34,37,39,e3] reported mean years of education.

Education level and subclinical CVD. Of the 26 studies, 16[9,18,19,23–25,26,29,31,33,35,38,40,e1,e2,e4,e5] reported education level (either duration or attainment) for individuals

Figure 2 Forest plot comparing low education vs high education and risk of subclinical cerebrovascular disease (CVD) features



Odds ratio (OR) < 1 = low education (<9 years) decreases risk of having features; OR > 1 = low education increases risk of having CVD features. Results are unadjusted unless stated otherwise. CI = confidence interval; SVD = small vessel disease. [a] Adjusted for age. [b] Adjusted for age, sex, race, hypertension, diabetes, and serum uric acid levels. [c] To avoid double-counting participants, this is not included in "all participants." [d] To avoid double-counting participants, this does not include lacune data from Farfel et al. (2013),[9] infarct data from Brayne et al. (2010),[18] and Mortamais et al. (2014).[26]

with subclinical CVD (WMH, microbleeds, lacunes, infarcts, and SVD).

Three studies[9,18,26] reported education and more than one marker of CVD. To avoid double-counting, participant data from only one CVD marker were included when calculating the ORs for all participants. We excluded infarcts from the first study[18] (unclear whether the infarcts were silent) and lacunes in the second[9] (captured in SVD score). The third study[26] had infarct and WMH data. Sensitivity analysis showed that exclusion of infarct data from this study resulted in an OR of 1.17 (95% CI 1.05 to 1.31, p = 0.003, figure 2). Exclusion of WMH data reduced the OR to 1.14 (95% CI 1.03 to 1.27, p = 0.01).

Further sensitivity analysis excluding 2 articles with unclear definitions of CVD markers[18,35] and 2 with the lowest quality score[9,18] did not alter results materially (OR 1.20, 95% CI 1.05 to 1.36, $p = 0.007$; OR 1.20, 95% CI 1.07 to 1.35, $p = 0.002$, respectively).

Subgroup analysis for individual CVD features (figure 2), including all 16 studies, showed lower educational level was associated with more WMH (6 studies,[6,29,33,40,42,45] n = 5,564, OR 1.24, 95% CI 1.05 to 1.47, $p = 0.01$) but no difference in infarcts (4 studies,[18,26,35,46] n = 5,184, OR 1.04, 95% CI 0.81 to 1.34), microbleeds (2 studies,[25,41] n = 3,618, OR 1.04, 95% CI 0.81 to 1.34), or lacunes (2 studies,[9,18] n = 1,465, OR 1.11, 94% CI 0.85 to 1.45). Low education was also not associated with SVD, which included multiple markers of CVD (3 studies,[9,38,46] n = 1,333, OR 1.36, 95% CI 0.93, 2.01).

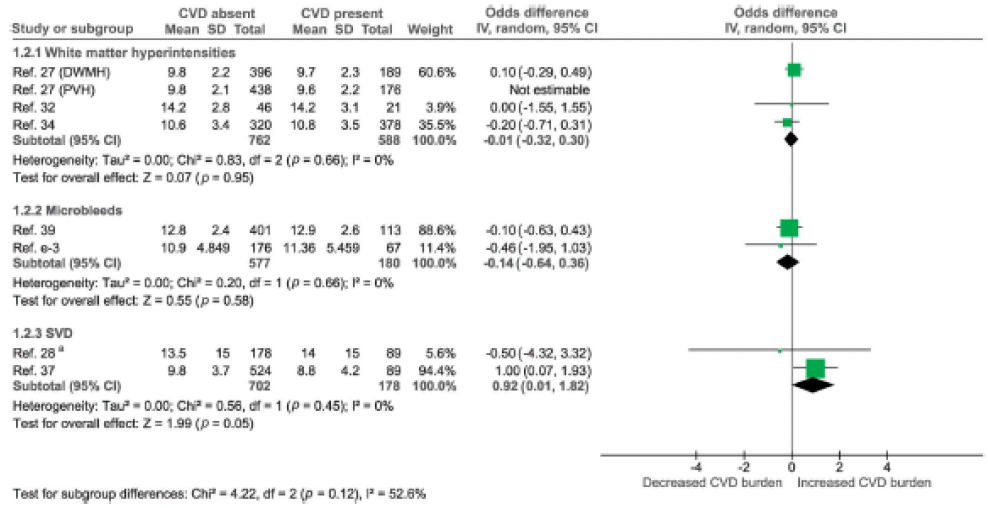
Four studies[19,23,31,44] (n = 949) could not be included in the meta-analysis due to the statistics reported. Two reported a significant correlation between education and deep WMH ($r = -0.149$, $p < 0.05$), PVH[19] ($r = -0.167$, $p < 0.05$, n = 243), and subclinical CVD[44] ($\beta = -0.258$, $p = 0.01$, n = 172) and 2 reported nonsignificant associations between education and overall WMH ($\beta = 0.43$, $p = 0.238$, n = 133), periventricular WMH ($\beta = 0.08$, $p = 0.598$, n = 133), deep WMH[23] ($\beta = -0.01$ $p = 0.964$, n = 133), and log-transformed WMH[31] ($F = 0.10$, $p = 0.74$, n = 401).

Mean years of education and CVD markers. Seven studies[27,28,32,34,37,39,43] (n = 3,016) reported mean years of education by presence/absence of several CVD markers (figure 3). Overall, mean difference in years of education did not differ between those with subclinical CVD and those without, either overall (7 studies, n = 3,016, MD = −0.07 years, 95% CI −0.19 to 0.34, $p = 0.59$), or when analysis was restricted to individual CVD markers. Heterogeneity between studies was low (I^2 5%, $p = 0.13$).

Mean volume of WMH in those with low and high education. There was no difference in mean WMH volume between those with high and low educational levels (4 studies[24,30,35,36]) (n = 4,330, MD = 0.02, 95% CI −0.02 to 0.07, $p = 0.24$, random effects, figure 4). There was substantial heterogeneity between studies (I^2 78%, $p = 0.003$) but the small number of studies (4) precluded producing a funnel plot to assess publication bias.

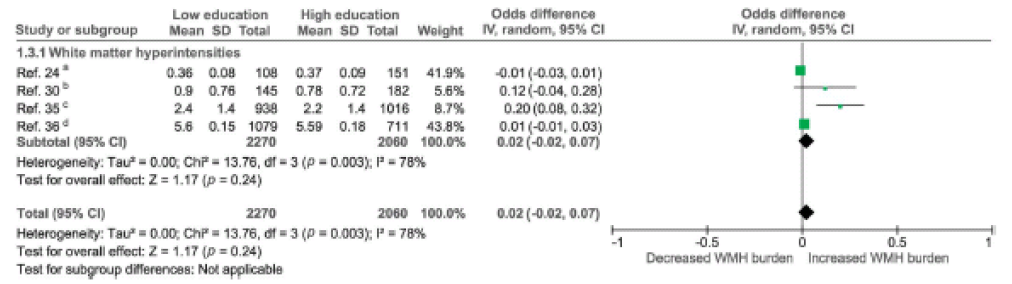
DISCUSSION WMH,[6] silent infarcts,[46] and microbleeds[47] in later life are independent risk factors for cognitive decline, dementia, and stroke. WMH and prior infarcts also independently reduce the chances of good recovery after stroke.[48] Therefore identifying factors that increase the risk of subclinical CVD in later life as early as possible is important to improve individual and population health and prevent dementia and stroke. Our meta-analysis is, as far as

Figure 3 Forest plot showing mean years of education for those with lower vs higher cerebrovascular disease (CVD) burden, random effects model for the mean difference



Negative mean difference = low education decreases white matter hyperintensities (WMH) volume; positive difference = low education increases WMH volume. CI = confidence interval; DWMH = deep white matter hyperintensities; PVH = periventricular hyperintensity. [a] Median years of education report.

Figure 4 Forest plot showing mean white matter hyperintensity (WMH) volume in those with low vs high levels of education, random effects model for the mean difference



Negative mean difference = low education (<high school) decreases WMH volume; positive difference = low education increases WMH volume. Results are unadjusted unless stated otherwise. CI = confidence interval. [a] Mean log WMH volume. [b] Mean WMH volume adjusted for age, sex, and total cranial volume. [c] Mean WMH density. [d] Mean WMH grade.

we know, the first to examine childhood IQ, childhood SES, education, and risk of subclinical CVD in later life. It suggests that higher cognitive ability in childhood, better SES, and longer duration of education predict lower risk of subclinical CVD in later life, with most information available for cognitive ability and education. Less vs more education increased the relative risk of having subclinical CVD by 17% relative to those with more education. Not all analyses were significant, but the samples available for some analyses were small and the direction of association was the same across all comparisons.

The literature had several limitations. Potential confounders were not well-reported and varied between studies. Frequency data were used to calculate several unadjusted ORs. Two studies[7,40] reported a significant effect after adjustment for vascular risk factors, but the paucity of studies precluded comparing adjusted with unadjusted results. The only study[19] on childhood SES did not adjust for current (adult) SES, although the latter is likely to influence later life CVD. A separate analysis showed a negative but nonsignificant association between adult SES and WMH.

Several studies reported significant differences in IQ or education among participants with and without MRI data.[13,24,28,31] Furthermore, participants in all but 3 articles were younger than 80 at the time of CVD assessment, thus possibly omitting the groups at highest risk for CVD.[49] We therefore may have underestimated the magnitude of early life effects on CVD features. Few studies provided clear working definitions of subclinical CVD. Cortical and subcortical infarcts were not distinguished (2 studies[26,45]) or were symptomatic or asymptomatic infarcts (2 studies[18,35]). However, on balance, these infarcts appeared likely to be asymptomatic and their omission did not influence the results. Lack of consistency in the definitions of CVD features may have resulted in similar lesions being classified differently across studies, hence our focus on overall CVD. Use of published standards for reporting vascular findings on neuroimaging[4] should facilitate future meta-analyses of imaging CVD.

Studies were mostly small, reflecting that MRI is time-consuming, expensive, and limits study participation: ongoing large cohort MRI studies will facilitate examination of these relationships in larger samples.

Our funnel plot did not identify publication bias, but publication bias may have influenced the results, as (unlike clinical trials) observational studies are not often registered, and analyses may be performed and not published. Furthermore, some studies may not report all collected data (e.g., omit some neuroimaging variables). If negative studies are unpublished, we will have overestimated the relationship between early life factors and CVD. However, many of the studies collected early life factors, particularly education, as a descriptive statistic, which may have reduced the likelihood of publication bias.

Our systematic review had limitations. We lacked resources to contact all authors for missing data. We specified 3 early life factors to review, and did not include studies on other, potentially relevant, influences (e.g., birthweight, nutrition). Most studies used neuroimaging assessment of CVD. We included 2 studies that assessed CVD pathologically but these were large population-based studies.[9,18] Classification of WMH and SVD varied between studies (low vs high or absent vs present), which may affect data interpretation. We were not able to correct for adult SES or lifestyle as this information was not available.

However, others have found that effects of childhood influences on overall mortality persist after correction for adult SES, giving no reason to think that the childhood influences seen here are solely due to unmeasured adult influences.[e10]

Strengths include a prespecified, published protocol, validated search strategy, double data extraction, adherence to guidelines, and exemplary systematic review and meta-analysis methods, including an established quality assessment scale. Finally, although some of the sample sizes were small, the total sample size for many analyses was reasonable, producing a comprehensive literature review and meta-analysis amassing data on 22,890 participants.

Childhood IQ, SES, and education are all closely related with likely interdependent effects on CVD. Children from disadvantaged backgrounds score worse on cognitive tests[e11]; those with higher IQ may be more likely to obtain further education; education may be a proxy for cognitive ability.[e12] A significant direct effect of childhood SES on WMH burden with no mediation by childhood IQ or education was reported in one study[19] but no other studies included more than one early life factor. Another study[9] reported that exposure to minimal amounts of schooling (1–4 years) appeared to be protective against development of CVD. Therefore, although reciprocal pathways among IQ, SES, and education are likely to be important, there may also be independent influences on later health. The current literature does not allow assessment of the independence of the 3 early life factors on later life CVD. This is a target for future research.

Positive early life factors can influence occupation, increase access to health care, and influence health literacy, disease self-management, and prevention. They may influence behaviors conducive to health (e.g., healthy eating) and reduce negative behaviors (e.g., smoking). This may in turn influence self-management of vascular risk factors (e.g., hypertension,[e13] obesity[e14]). Alternatively, education and IQ may reflect brain integrity or resilience[e15]: white matter structural integrity is better and the cortex is thicker in 70-year-olds who scored higher on IQ tests at age 11, which may protect against accumulating CVD,[e12,e16] hence reducing the risk of stroke and dementia.[6] These possibilities remain to be tested.

The causes of SVD are heterogeneous: white matter diseases represent a wide spectrum whose etiology and pathophysiology remain unclear. WMH are highly heritable[e17] and associated with familial longevity[e18]; however, genome-wide association studies have thus far demonstrated few convincing genetic associations for WMH and monogenic SVDs (e.g., cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy) are rare. WMH are common in otherwise healthy older people and although previously considered part of normal aging, numerous studies have demonstrated important clinical associations,[e19–21] including trebling the risk of stroke and doubling the risk of dementia. Increasing evidence suggests that WMH should not be overlooked as an inevitable consequence of aging and but rather regarded as a measure of CVD. Furthermore, vascular risk factor reduction can delay progression of WMH in patients with CVD,[e22,e23] making it a viable target for clinical intervention.

Our findings suggest an important, albeit small, effect of early life factors on covert brain vascular disease in later life. Whether this reflects better brain resilience or integrity, or lifestyle or vascular risk factors, requires further research. All subclinical features assessed here increase risks of cognitive decline, dementia, and stroke,[6] independently worsen chances of recovery after stroke,[e8] and may provide a mechanistic link between early life factors and risk of stroke or dementia in later life. Health disparities are well-known.[e24] That the effects of such disparities appear to persist across decades of life highlights the importance of identifying modifiable factors that may be targets for future social policy interventions. Our results support the view that access to quality education may reduce cerebrovascular disease and improve population health in later life. Efforts to understand factors that may contribute to late life brain health, from the earliest stages in life, are important targets for future research and public health policy.

AUTHOR CONTRIBUTIONS

E.V.B. carried out the systematic literature search, extracted the data, performed the meta-analysis, and drafted the manuscript. C.A.M. drew up the protocol, carried out the search, extracted data, and performed the meta-analysis, checking, and editing. V.C. and S.D.S. discussed the protocol and search, reviewed articles that were uncertain, advised on the meta-analysis and interpretation of data, and reviewed and edited the manuscript. V.C. helped to obtain funding. J.M.W. conceived the project, obtained funding, managed the project, designed the protocol, and checked the search strategy, reviewed uncertain articles and checked data, advised on the meta-analysis and interpretation of data, and reviewed and edited the manuscript, and is the guarantor of the project. All authors approved the final draft of the manuscript.

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DISCLOSURE

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Early life risk factors for cerebrovascular disease: A systematic review and meta-analysis

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Education, Socioeconomic Status, and Intelligence in Childhood and Stroke Risk in Later Life

A Meta-analysis

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Background: Stroke is the second most common cause of death, and a common cause of dependency and dementia. Adult vascular risk factors and socioeconomic status (SES) are associated with increased risk, but less is known about early life risk factors, such as education, childhood SES, or intelligence (IQ).

Methods: We comprehensively searched Medline, PsycINFO, and EMBASE from inception to November 2015. We included all studies reporting data on >50 strokes examining childhood/premorbid IQ, SES, and education. Two reviewers independently screened full texts and extracted and cross-checked data, including available risk factor adjustments. We meta-analyzed stroke risk using hazard ratios (HR), odds ratios (OR), and mean differences (MD). We tested effects of study and participant characteristics in sensitivity analyses and meta-regression, and assessed heterogeneity and publication bias.

Results: We identified 90 studies examining stroke risk and education (79), SES (10), or IQ (nine) including approximately 164,683 stroke and over 5 million stroke-free participants. Stroke risk increased with lower education (OR = 1.35, 95% CI = 1.24, 1.48), SES (OR = 1.28, 95% CI = 1.12, 1.46), and IQ (HR = 1.17, 95% CI = 1.00, 1.37) in studies reporting point estimates, with similar associations for MD. We found minimal publication bias. Between-study heterogeneity was partly explained by participant age and case ascertainment method.

Conclusions: Education, childhood SES, and intelligence have modest but important associations with lifetime stroke, and hence dementia, risks. Future studies distinguishing between the individual and combined effects of education, childhood SES and intelligence are needed to determine the independent contribution of each factor to stroke risk. See video abstract at, http://links.lww.com/EDE/B210.

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Stroke is the second most common cause of death worldwide[1,2] and the most common cause of dependency in adults in the developed world.[3] The absolute number of strokes per year, prevalence, and global burden are large and increasing.[2] Among the 16.7 million people who have a first stroke each year worldwide,[4] a third will die and a third of survivors will have cognitive impairment or dementia.[5] Reduction in stroke is therefore likely also to reduce dementia.

Vascular risk factors in adulthood, such as hypertension, diabetes, and smoking, are associated with increased risk of stroke and are established targets for prevention, but only explain part of the variance in stroke risk.[6] Poor socioeconomic status (SES) in adulthood,[7] and declining cognition[8] in later life are recognized to increase stroke risk. Factors such as childhood education, SES, and intelligence (IQ) have been associated with increased risk of cardiovascular disease,[9–12] chronic adult diseases,[13] and death from stroke in adulthood,[14] but with mixed findings, limited information specifically on stroke[14,15] and no meta-analysis to determine overall effects. Two reviews[9,14] found associations between low childhood SES and increased risk of stroke in some but not all included studies, but did not perform a meta-analysis.

To address the hypothesis that less education, lower SES, or lower IQ in childhood affect stroke risk in later life, and if so by how much, we performed a systematic review and meta-analysis of all available data.

METHODS

We used the Meta-analysis of Observational Studies in Epidemiology (MOOSE)[16] and Preferred Reporting

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Data are available on request.

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Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines[17] and prospectively registered the protocol, including search methods, with PROSPERO (registration number: CRD42015016701).

Search Methods

We developed and tested a search strategy (see eDocument 1; http://links.lww.com/EDE/B199, which details the search strategy used for MEDLINE) with an experienced librarian to identify studies that examined early life factors (education, childhood SES, and childhood/premorbid IQ) and cerebrovascular disease including clinically overt (i.e., stroke, cognitive impairment, depression) or "silent" features detected on imaging or pathology (see Backhouse et al.[18]). Here we report the data on stroke.

We searched MEDLINE (1966 to present), PsycINFO (1806 to present), and EMBASE (1980 to present) for papers published up until end November 2015 using OVID SP UI03.16.00.110. We checked reference lists of identified papers and hand searched the previous five years of *Stroke*, *Neurology,* and *International Journal of Epidemiology*. We contacted authors for clarification of results where required but not routinely due to resource availability.

A single reviewer screened each title and abstract; uncertain papers were cross-checked by the other reviewer or examined in more detail. Eligible full text articles were assessed independently by both reviewers. Disagreements regarding inclusion were discussed between the two reviewers and the review team.

We compared duplicate publications on the same cohort for each early life factor. Based on sample size (largest), publication year (most recent), and relevance of outcome reported, a single paper per study was selected to avoid duplication of participants.

Study Criteria

Studies that provided data on stroke in adulthood in relation to one or more of the three early life factors were included. We included general IQ measures collected up to early adulthood. Estimates of IQ in youth, determined using a valid tool in older subjects (e.g., National Adult Reading Test (NART),[19] Wechsler Test of Adult Reading (WTAR),[20] etc.) were also included based on their strong relationship to childhood IQ.[21] Indicators of childhood SES such as parental education or occupation and housing conditions collected postpartum were included. All measures of education (years, highest level attained) were included.

"Stroke" was defined as a diagnosis based on clinical examination, neuroimaging, self-reported, or a diagnosis extracted from centralized health statistics (e.g., hospital and death registers etc.). Ischemic stroke, being the commonest type, was the primary outcome. We included studies examining a combination of ischemic, hemorrhagic stroke, and transient ischemic attack (TIA) as these samples consisted predominantly of ischemic stroke patients. We excluded studies of hemorrhagic stroke or TIA only as these were too small and infrequent.

We considered papers written in any language, containing relevant primary data and published in full in peer-reviewed journals. We excluded review articles, abstract-only publications, animal studies, children ages <18 years only, stroke mortality only, fewer than 50 stroke cases or that focused on a specific patient subpopulation (e.g., Parkinson's Disease etc.).

Data Extraction and Quality Assessment

One of two reviewers performed data extraction, with each extraction cross-checked by the other reviewer; a sample were cross-checked by the remaining members of the review team. We extracted data on study design and setting, participants, definitions of early life factors and stroke, numbers with and without stroke, the relevant statistic (odds ratio [OR], hazard ratio [HR], relative risk [RR] etc.), and any confounding variables such as hypertension, adult SES, etc.

We quality assessed the included studies,[22] based on six factors; representativeness of study sample, attrition, description, and reliable measurement of early life factor and stroke, inclusion of confounding variables and appropriateness of statistical analysis. Each aspect was rated on a four-point scale (yes/4, partly, no, and unsure/1), with maximum score (best quality) of 24.

Statistical Analysis

We grouped the included papers by reported outcome statistic (e.g., HR, OR, RR, or mean) for meta-analysis. We chose the outcome variable with the most data, and that represented a similar level of education where more than one was offered. We defined "low education" as 8–10 years of full time education or below and "high education" as 11 years and above. Most papers reporting childhood SES used father's or head of household's occupation, classed as manual or non-manual, to indicate low or high SES which we therefore used in meta-analysis. We used parental education level and financial troubles in childhood (yes/no) where father's occupation was not available. Most papers reporting childhood IQ reported a score on a specific test or compared quartiles. We used the study's definition of lower versus higher IQ. We compared the lowest and highest IQ when no overall HR was reported.

We standardized all results to represent a reference level of high education, IQ, or SES. HRs, ORs, RRs, and mean differences (MD) were used to compute the overall effect and 95% confidence intervals (CIs) using Review Manager V.5.3.14. Where no ratio was reported, we used frequency data to calculate the OR. Where possible, we used outcomes adjusted for vascular risk factors or other key variables (listed in footnotes in figures). We estimated absolute differences in stroke rates per 1,000 population using the rates by education, childhood SES, or IQ category where reported. To account for an expected high level of heterogeneity, we used a random effects model. We assessed heterogeneity using the I^2 statistic and publication bias using a funnel plot.

We prespecified subgroups (adjusted versus unadjusted results, participant age and sex hospital/outpatient clinic, including case–control design, versus population sampling method, outcome measurement, and first only versus recurrent/unspecified stroke) to test whether any of these modified the association with education, IQ, or childhood SES in sensitivity analyses and also conducted meta-regressions using the "metafor" package[25] in R[24] to examine if any of these subgroups explained any variance.

RESULTS

The search identified 19,180 titles and abstracts, after removal of duplicates (Figure 1), from which we identified 1,217 full text articles. Of these, 905 were excluded, the main reasons being inappropriate outcome (e.g., not reporting stroke separately from other disease outcomes), followed by absence of analysis of early life factor in direct relation to stroke. We identified 90 papers which examined early life factors and risk of stroke (see Table and eTable 1a–c; http://links.lww.com/EDE/B199, which includes details of included papers). Although most Continents were represented by one or more studies, most studies took place in North America or Europe.

Quality Assessment and Publication Bias

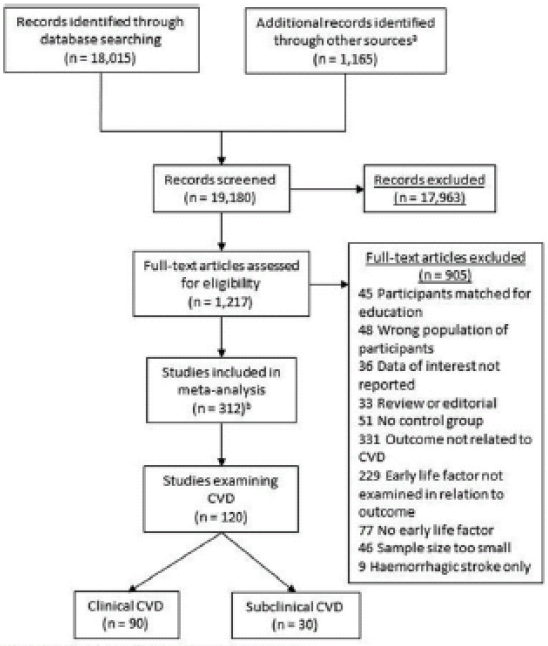
The quality of the included papers was good, with scores from 18 to 24/24 (median = 22). Sample representativeness was the lowest scoring subscale, with statistical analysis being the highest scoring (see eFigure 3; http://links.lww.com/EDE/B199, which shows frequencies by subscale).

All analyses were examined for publication bias. Little evidence of was found in analyses where there were sufficient numbers of studies for publication bias to be accurately assessed (see eFigure 4a–c; http://links.lww.com/EDE/B199, which show funnel plots for assessment of publication bias).

Education and Risk of Stroke In Adulthood

We included 79 studies,[11,25–102] reported in 108 papers (total n = 2,881,067), examining education and risk of stroke (see eTable 1a; http://links.lww.com/EDE/B199, which includes details of included papers). Thirty-one papers[66–68,70–72,74–77,80–89,91-101] reported adjusted results, of which 16[68,70,72,76,81,83,84,86,89,92-96,99,100] adjusted for vascular risk factors.

Twenty-five papers[41–65] reported frequencies of stroke by duration of education. We used these frequencies to calculate unadjusted ORs, which we analyzed with 19 other papers[66–84] that reported ORs (total 73,886 strokes and



[a]Includes hand-searching and scanning of reference lists
[b]Includes papers which examine post-stroke cognitive impairment and depression as outcomes
CVD indicates cerebrovascular disease

FIGURE 1. PRISMA flowchart of search and study selection.

TABLE. Summary of Included Papers (for Individual Details See eTable 1; http://links.lww.com/EDE/B199)

n	Education	Childhood SES	Childhood IQ
Number of studies identified	108	15	13
Number of studies included	79	10	9
Study setting			
Population	48	8	6
Hospital	22	1	3
Community	5	1	0
Outpatient clinic	9	0	0
Total number of stroke patients	141,788	13,210[a]	9,685
Total number of nonstroke patients	2,572,839[b]	1,318,962[a]	1,200,267
Age range of included studies	18–88	30–80	36–77
Quality Score[c]	22 (2)	22 (1.5)	22 (2.5)

Some studies fall into multiple categories.
[a]Data not reported for one study.
[b]Data not reported for three studies.
[c]Median (interquartile range).
SES indicates socioeconomic status.

2,324,944 stroke-free participants). Mean years of education was reported in 16 papers[25–40] (3,209 strokes and 19,712 stroke-free participants), 13 reported HRs[11,90–101] (7,871 strokes and over 207,336 stroke-free participants), and five reported RRs[85–89] (56,593 strokes and over 18,061 stroke-free participants [note that in all analyses the true denominator is larger than the number shown because not all studies reported the number of stroke-free participants]).

Overall, less versus more education was associated with an increased risk of stroke (OR = 1.35, 95% CI = 1.24, 1.48, I^2 = 96%; MD = 0.66, 95% CI = 0.31, 1.01, I^2 = 77%; HR = 1.33, 95% CI = 1.17, 1.53, I^2 = 70%; RR = 1.35, 95% CI = 1.09, 1.67, I^2 = 90%; Figure 2A, B). Based on included studies with relevant data (n = 46), this relative increase of 33%–39% was equivalent to an absolute increase in stroke of 3.5/1,000, that is, (when expressed as whole numbers) for every 2,000 people who only completed education up to high school level (or 11 years), 7 more will have a stroke compared with people with college or university education (>11 years). There was between-study heterogeneity for all comparisons, ranging from 76% to 96%. One study[102] reported a stroke prevalence ratio for those with higher education (PR = 0.9, 95% CI = 0.6, 1.1; 229 strokes and 2,786 stroke-free participants), so could not be included in the meta-analysis.

In sensitivity analyses, we examined education and stroke risk (see eFigure 5a–j; http://links.lww.com/EDE/B199, which includes forest plots for sensitivity analyses). Use of adjusted versus unadjusted risk ratios, participants' age, recruitment through hospitals/outpatient clinics, including case–control design, versus population cohorts, stroke ascertainment using clinical examination/neuroimaging versus self-report/centralized health data, participant sex and first only versus recurrent/unspecified stroke, did not explain between-study heterogeneity (See eFigure 5d–j; http://links.lww.com/EDE/B199). Meta-regression, possible on 41 studies, did not identify any study or participant characteristics that altered the relationship between education and stroke risk.

Childhood SES and Risk of Stroke In Adulthood

Ten studies,[11,63,84,89,98,103–107] reported in 15 publications (total n = 1,354,899), examined childhood SES and stroke (see eTable 1b; http://links.lww.com/EDE/B199, which includes details of included papers). Over 13,210 stroke and 1,318,962 stroke-free participants were included ages 30–70 years old at the time of follow-up or stroke. One study[103] did not provide the number of stroke and stroke-free participants (total n = 11,106). Frequencies were used to calculate ORs for five studies.[63,89,104–106] One paper adjusted for vascular risk factors,[84] one for adult SES,[98] and two for demographic variables.[98,107]

We meta-analyzed three studies[11,98,107] reporting HRs (3,240 strokes, 73,644 stroke-free participants) and six[63,84,89,104–106] reporting ORs (9,970 strokes, 1,245,318 stroke-free participants) for childhood SES and stroke. Subjects with lower childhood SES (i.e., father's occupation manual) had an increased risk of stroke compared with those with higher (i.e., nonmanual father's occupation) SES (HR = 1.31, 95% CI = 1.03, 1.68, I^2 = 88%; OR = 1.28, 95% CI = 1.12, 1.46, I^2 = 56%; Figure 3). Based on included studies with relevant data (n = 6), this relative increase of 28%–32% was equivalent to an absolute increase of 0.3/1,000 strokes, i.e., (when expressed as whole numbers) for every 10,000 people whose fathers had manual jobs, three more will have a stroke compared with people whose father's had nonmanual jobs. Removal of one large study[105] reduced the heterogeneity substantially (OR = 1.36, 95% CI = 1.30, 1.42, I^2 = 0%).

One study[103] reported the stroke rate by 10,000 person-years by father's occupational class so could not be meta-analyzed, but showed that lower versus higher father's occupational class was associated with a higher stroke rate (7.8 per 10,000/yr vs. 2.3 per 10,000/yr; P = 0.001).

Meta-regression on five studies found that studies ascertaining stroke using centralized health statistics versus direct examination were more likely to find that lower SES increased stroke risk (β = –0.21; P = 0.005).

Childhood IQ and Risk of Stroke In Adulthood

Nine studies,[11–13,39,63,108–111] reported in 13 studies (total n = 1,209,952), examined childhood/premorbid IQ and stroke (see eTable 1c; http://links.lww.com/EDE/B199, which includes details of included studies). Five studies[11,12,63,108,110] adjusted for confounders, of which three adjusted for vascular risk factors.[11,63,110]

Six studies[11–13,63,108,110] measured IQ in childhood/early adulthood and three[39,109,111] estimated premorbid IQ in adulthood using the NART resulting in 9,685 strokes and 1,200,264 stroke-free participants ages 36–77 years old at the time of follow-up or stroke.

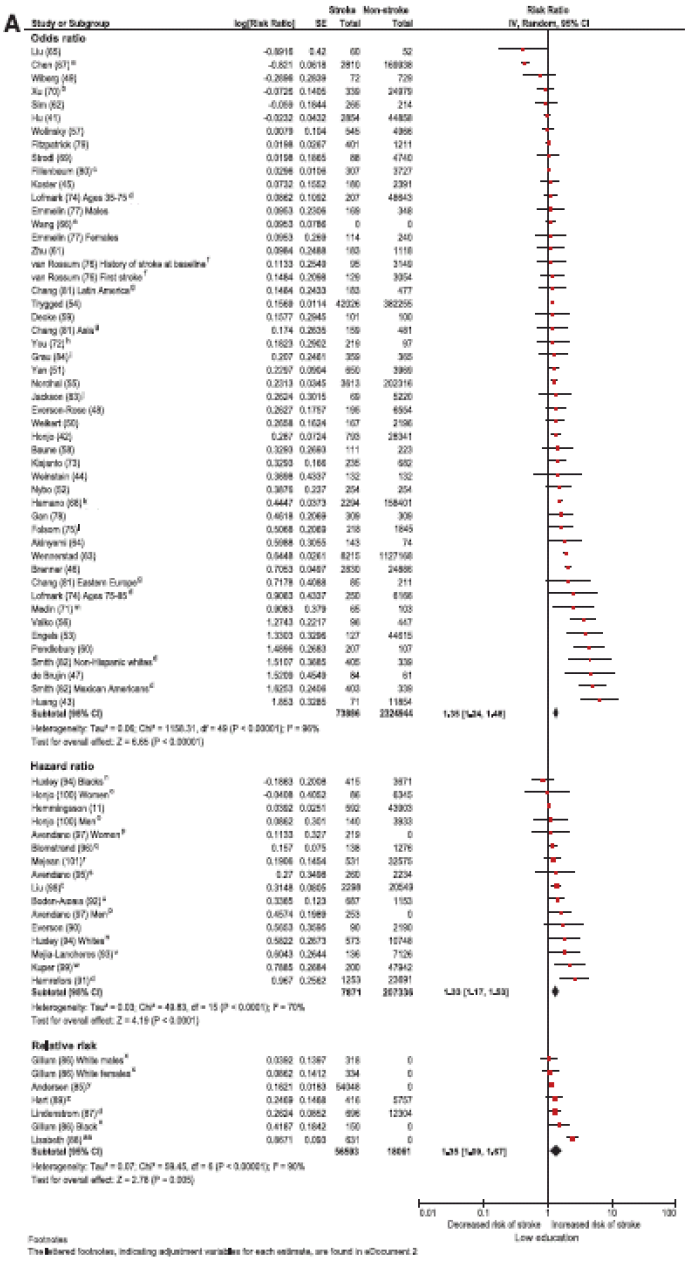


FIGURE 2. (*Continued*)

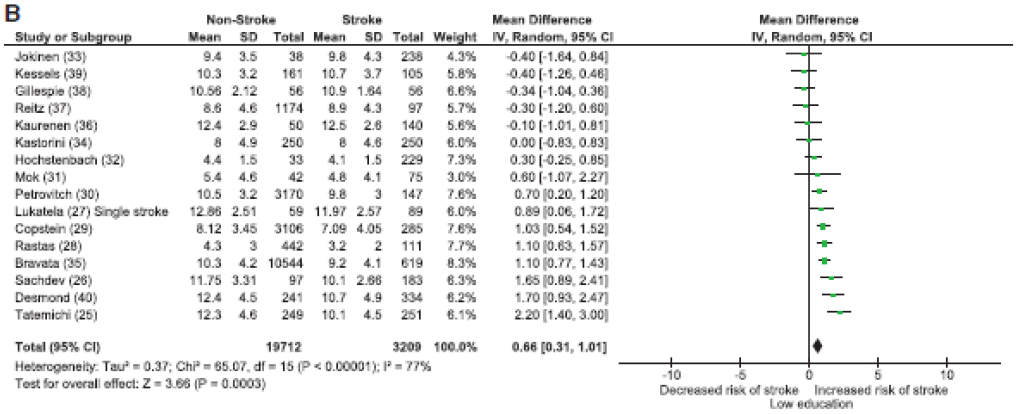
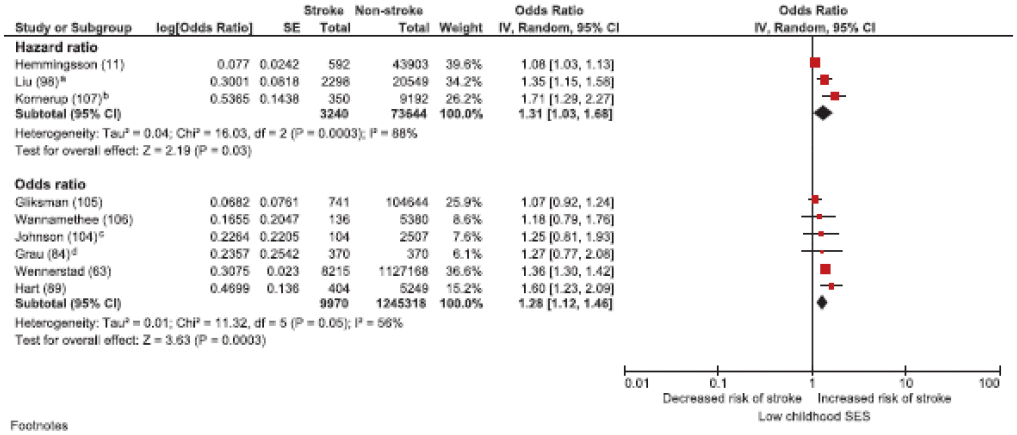


FIGURE 2. A, Education attainment (low versus high) and risk of stroke, risk ratio (OR, HR, and RR), random effects model (risk ratio <1 indicates low education decreases risk of stroke; >1 = low education increases risk of stroke). B, Education attainment in mean years of education in persons with and without stroke, random effects model for the mean differences (negative mean difference = lower education decreases risk of stroke and positive mean difference = higher education decreases risk of stroke). Figure is available in color online.



Footnotes
[a] Adjusted for age, race, ethnicity, gender, marital status, adulthood SES, smoking status, body mass index and chronic conditions
[b] SES defined by financial problems in childhood. Adjusted for age and sex
[c] SES defined by Father's highest level of education
[d] Adjusted for hypertension, diabetes, hyperlipidemia, previous stroke/TIA, PAD, smoking, alcohol abstinence and consumption and leisure time sports activity
NOTE: Studies without footnotes report unadjusted results

FIGURE 3. Childhood socioeconomic status (low versus high) and risk of stroke, risk ratio (HR, OR), random effects model (risk ratio <1 indicates low SES decreases risk of stroke; >1 = low SES increases risk of stroke). Figure is available in color online.

We meta-analyzed five studies[11,12,63,108,110] (9,087 strokes, 1,191,612 stroke-free participants) reporting HRs and three[39,109,111] (322 strokes, 305 stroke-free participants) reporting the average IQ score and risk of stroke. In subjects with a lower versus higher childhood IQ, stroke risk was increased (HR = 1.17, 95% CI = 1.00, 1.37, I^2 = 55%; MD = 6.83, 95% CI = 2.11, 11.55, I^2 = 72%; Figure 4A, B). Based on included studies reporting the relevant data (n = 3), this 17% increase in relative risk was equivalent to an increase in absolute risk of 0.3/1,000, that is, (when expressed as whole numbers) for every 10,000 people whose childhood IQ was lower than the population average, three more will have a stroke compared

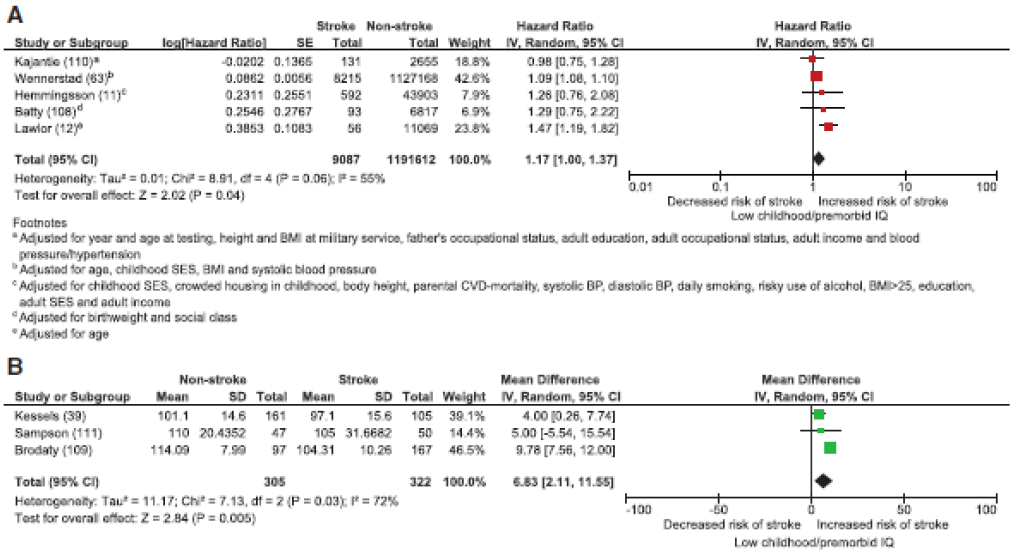


FIGURE 4. A, Childhood/premorbid IQ (low versus high) and risk of stroke, hazard ratio, random effects model (hazard ratio <1 indicates low IQ decreases risk of stroke; >1 = low IQ increases risk of stroke). B, Childhood/premorbid IQ by mean IQ score in persons with and without stroke, random effects model for the mean difference (negative mean difference = lower IQ decreases risk of stroke and positive mean difference = lower IQ increases risk of stroke). Figure is available in color online.

with children whose childhood IQ was higher than the average. The remaining study[13] reported an OR which could not be included in the meta-analyses. Consistent with the other studies, it demonstrated that higher IQ was associated with decreased stroke risk (OR = 0.85, 95% CI = 0.74, 0.99) after adjusting for demographic and SES factors. Removal of one large study[12] reduced heterogeneity to zero (overall HR = 1.09, 95% CI = 1.08, 1.10).

DISCUSSION

This meta-analysis of all available literature shows these early life factors to be consistently associated with increased stroke risk in adulthood. Having <11 versus ≥11 years of education was associated with an increase in relative risk of stroke of about a third. Similarly, lower childhood SES and IQ were both associated with 17%–32% relative increases in stroke risk. These relative risks translated to absolute increases in stroke risk in adulthood of approximately 3.5/1,000 for lower versus higher education and 0.3/1,000 for lower versus higher childhood SES and IQ. These apparently small absolute effects are substantial when considered in terms of the huge global burden of stroke—for example, for every 2,000 people living in a country where, say, most people leave full time education after high school, there may be about seven more strokes over a lifetime than, say, in a country where many people continue in education beyond high school level. Or, for every 10,000 people in a country where most fathers had manual jobs, there may be about three more strokes in a lifetime than in a country where many people's fathers had nonmanual jobs. In a country of 50 million people most of whom leave education before or at completion of high school, 175,000 more of them might expect to have a stroke in their lifetime than in another country of 50 million people most of whom complete a college or university education. These simple illustrations are only intended to provide estimates of the potential magnitude of absolute effects, as they do not account for age at stroke (which may be younger in those exposed to the higher risk), and should be viewed with caution.

Our findings build on previous reviews[9,14] suggesting that poorer conditions in childhood were associated with a higher stroke risk in adulthood. However, there has been no previous comprehensive meta-analysis of any of the three factors and stroke risk such as performed here.

Many studies included relatively young participants yet the median age for stroke is 72 and incidence rises with age.[112] Most participants in studies of childhood IQ and SES were younger than the typical age of stroke, so further research is needed to determine whether the risk increases further with age. A study (n = 470) published after our search cut-off[113] found that poorer childhood SES was associated with a higher stroke risk in subjects of mean age = 66.5. Despite the paucity of studies examining older participants, there is clear evidence

that early life factors contribute to the risk of stroke, even in younger adults.

Many studies did not adjust for known risk factors, such as hypertension, smoking, or diabetes. In those that did, there was considerable variation in the number and type of risk factors. Although risk factor-adjusted results showed a lower stroke risk compared with unadjusted results, the overall effect remained significant. Other factors, for example, birth weight or childhood nutrition were not considered as they were unavailable for most studies.

Differences in the measurement of early life factors and stroke ascertainment may have contributed to heterogeneity. Many larger studies relied on centralized health statistics, which may be less specific than clinical examination and neuroimaging, although may avoid other source of bias. Studies using centralized health statistics showed a lower stroke risk compared with those using clinical examination and neuroimaging. Additionally, we focused on ischemic stroke due to the small number of studies with >50 strokes in hemorrhagic stroke studies. One review suggested that the effect of childhood SES was higher in hemorrhagic stroke but did not perform a meta-analysis.[9]

It is likely that the early life factors are inter-related but very few studies presented information on more than one factor simultaneously. Many studies use education as a proxy for childhood IQ, as those with higher IQ are more likely to pursue higher education. The closeness of the two variables has been widely debated.[114] Only four identified studies included more than one early life factor, of which two accounted for early life factors in analysis[11,63] and found that the relationship between lower childhood IQ and increased stroke risk in middle-age men remained when controlling for education. Other studies suggest that a strong association between childhood IQ and later life disease risk even when accounting for other childhood factors such as SES.[10,12] Childhood SES is related to risk of death in adulthood independent of adult SES,[115] and the childhood SES relationship to adult stroke risk remained in the one study that adjusted for adult SES.[98]

Our systematic review had limitations. We lacked resources to contact authors for missing data. Due to available data, absolute risks were calculated on a subset of papers, a further reason for caution. The sensitivity analyses and meta-regressions were not able to account for much of the heterogeneity. Although some studies were performed in the Asia Pacific Region and Africa, most studies were based in Europe or North America; social and educational disparities may vary in other world regions but lack of relevant data precluded a sensitivity analysis of racial or geographical differences.

There were also strengths. The importance of quality assessment is widely recognized[116]; however, there is no agreed method of assessment.[22,117] Nonetheless, two reviewers assessed each study independently using an established scale,[22] finding high study quality with minimal bias and strong statistical methodology. We registered the protocol, used state-of-the-art methodology, found all articles thought to be relevant and included non-English papers, thus the review included approximately 164,683 strokes and over 5 million stroke-free participants, with at least 1.2 million subjects or more in analysis of SES and IQ.

IMPLICATIONS AND CONCLUSIONS

There are several possible explanations for the observed relationships. Individuals with higher childhood SES and intelligence may pursue and have better access to higher education, hence higher paid, safer jobs. This may encourage better health and lifestyle behaviors including exercise, diet, and self-management of vascular risk factors, resulting in decreased stroke risk. Alternatively, positive factors in early life may be associated with greater brain resilience, allowing more subclinical vascular brain damage to be sustained before clinical stroke occurs; further research is required to determine if this latter hypothesis is likely.

We show a consistent relationship between lower childhood/premorbid IQ, SES and education, and increased risk of stroke. Disparities in health and social equality have been widely discussed (e.g., Marmot Report[118]). Because stroke is a risk factor for dementia,[119] future studies should examine the literature to see whether the early life factors influence risk of dementia. Additionally, future studies should distinguish between lifestyle and vascular risk factors, examine the individual and combined effects of intelligence, SES and education to determine the independent contribution of each factor to stroke (and dementia) in later life.

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RESEARCH ARTICLE

Cognitive ability, education and socioeconomic status in childhood and risk of post-stroke depression in later life: A systematic review and meta-analysis

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Abstract

Background

Depression after stroke is common and is associated with poorer recovery. Risk factors such as gender, age and stroke severity are established, but it is unclear whether factors from earlier in life might also contribute.

Methods

We searched MEDLINE, PsycINFO, EMBASE and meta-analysed all available evidence on childhood (premorbid) IQ, socioeconomic status (SES), education and stroke in adulthood. We included all studies reporting data on >50 patients, calculating overall odds ratios (OR), mean difference, correlation, 95% confidence intervals (CI) and 95% predictive intervals (PI) using random effects methods. We quality assessed all studies, performed sensitivity analyses, assessed heterogeneity and publication bias.

Results

We identified 33 studies including 2,664 participants with post-stroke depression and 5,460 without (314 participants not classified). Low education (< = 8 years) was associated with post-stroke depression in studies which defined depression as score of mild and above on a depression rating scale (OR 1.47 95% CI 1.10–1.97, p<0.01) but not in studies where depression was defined as severe depressive symptoms or a clinical diagnosis of major depression (OR 1.04 95% CI 0.90–1.31, p = 0.60). Low education was not associated with an increased risk for post-stroke depression in studies that adjusted for age and sex (OR 0.86 95% CI 0.50–1.48 p = 0.58). Those with post-stroke depression had fewer years of education than those without post-stroke depression (MD 0.68 95% CI 0.05–1.31 p = 0.04).

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Few studies adjusted for vascular risk factors or stroke severity. Heterogeneity between studies was moderate and was partly explained by severity of depression. In the one study identified premorbid IQ did not differ between those with post-stroke depression (mean IQ 10.1.8 SD 9.8) vs those without (mean IQ 104 SD 10.1). There were no studies that examined childhood socioeconomic status and risk of post-stroke depression.

Conclusions

Having less education is associated with an increased risk of post-stroke depressive symptoms but with large confidence intervals and heterogeneity. Future studies should explore the relationship between early and late life risk factors to improve risk identification and to target prevention and treatment strategies.

Introduction

Stroke is the commonest cause of dependency in adults in the developed world [1] and also causes cognitive, physical and psychiatric disabilities. Depression is one of the most common neuropsychiatric disturbances following stroke, occurring in approximately 31% of patients during the first 5 years [2]. People with post-stroke depression experience greater impairment, including worse cognitive impairment, more substantial reductions in activities of daily living, and increased mortality [3] compared with non-depressed stroke patients. Post-stroke depression can severely impair physical rehabilitation and recovery [3].

Several risk factors for post-stroke depression have been proposed. These include gender, medical and psychiatric history [3, 4], age, and social support [4] as well as factors relating to the stroke such as severity and degree of resulting disability [3]. However, evidence supporting these factors is mixed and they only explain some of the variance in post-stroke depression. Factors from earlier in life may also be important. Two recent meta-analyses [5, 6] reported that low childhood cognitive ability, low childhood socioeconomic status (SES) and low education were associated with an increased risk of stroke and subclinical cerebrovascular disease on neuroimaging or at post mortem. Few studies have specifically examined the relationships between these childhood factors and post-stroke depression, but it is possible that an association exists via the relationships between early life factors and vascular disease. A previous review [7] of 10 studies found no association between education and post-stroke depression. However, this review only included papers published in English between 1995 and 2012 which directly analysed education as a risk factor, and did not perform a meta-analysis.

To address the question of whether childhood cognitive ability, SES or education affect the risk of post-stroke depression in later life, we performed a systematic review and meta-analysis of all published literature.

Method

The methodology of this systematic review has been described previously [5, 6]. We used the PRISMA and MOOSE guidelines [8] (see S1 Table), and registered the protocol prospectively on Prospero (registration number: CRD42015016701).

Using a detailed search strategy (Appendix in S1 File) we searched PsycINFO (1806-present), MEDLINE (1966-present) and EMBASE (1980-present) for papers published until 6 April 2017 using OVID SP UI03.16.00.110. We also checked reference lists of identified papers

and relevant review papers and hand searched the previous five years of *Stroke*, *Neurology* and *International Journal of Epidemiology*.

Each abstract and title were screened by one reviewer and all potentially relevant texts were independently screened by two researchers (EB or CM) for relevance. Disagreements regarding eligibility were resolved through discussion between authors.

We included studies that provided data on one or more early life factors (education, social class, IQ) in relation to a diagnosis of depression or measurement of depressive symptoms following stroke. We defined depressive symptoms as any measurement of mood using a valid scale conducted at any time following a stroke. Valid scales included the Beck's Depression Inventory, the Montgomery Asberg Depression Rating Scale (MADRAS) and the Hamilton Depression Rating Scale (HDRS) (higher score indicates worse depression/depressive symptoms). A diagnosis of major depression according to classification systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) was also included. We included general intelligence (IQ) measurements performed up to age 18 and estimates of premorbid IQ using valid tools (e.g. the National Adult Reading Test (NART)). All measures of childhood education were included (duration, attainment). We included childhood SES measures such as parental occupation or education.

We excluded papers with less than 50 patients, those focusing on a particular non-stroke patient population (e.g. Multiple Sclerosis), without primary data, not reporting data on humans aged 18 or over, or abstract only publications. We considered papers in any language. We used double data extraction conducted by two researchers.

We quality assessed the included studies on six potential sources of bias [9]: representativeness of the sample to the general population, whether study attrition was reported, how education and post-stroke depression were measured, whether results were adjusted for confounders and appropriateness of the statistical analysis. We rated each of these on a 4-point scale (corresponding to unclear, no, partly, yes) with a maximum score of 24. We counted each study only once, being careful to avoid double counting where more than one paper referred to the same study.

We standardised all education results to represent a reference level of high education, based on each paper's categorisation of education in the majority of papers. Low education was defined as approximately 6–8 years (or less than high school) and high education as 9 years and above (or high school and above).

We used Review Manager V.5.3 to calculate overall odds ratios (OR) or mean differences (MD) and 95% confidence intervals using a random effects model. Where multiple statistics were reported, we used the one that maximised data available for meta-analysis. Where possible, we used the results adjusted for depression or vascular risk factors over crude results. Where necessary, we calculated odds ratios from frequency data and we analysed correlation coefficients using the package 'metacor' for R V.3.0.1. We analysed papers which reported means years of education in a separate group. We assessed heterogeneity using the I^2 statistic and publication bias with funnel plots. We further calculated 95% prediction intervals which incorporates existing heterogeneity and quantifies the likely range of associations between education and depression in similar future studies [10].

We performed post-hoc sensitivity analyses on several clinically important subgroups and factors previously reported to be associated with post-stroke depression.

Results

We identified 24,289 titles and abstracts after removal of duplicates (Fig 1), from which we identified 1,314 full text articles. The commonest reason for exclusion was no measurement of

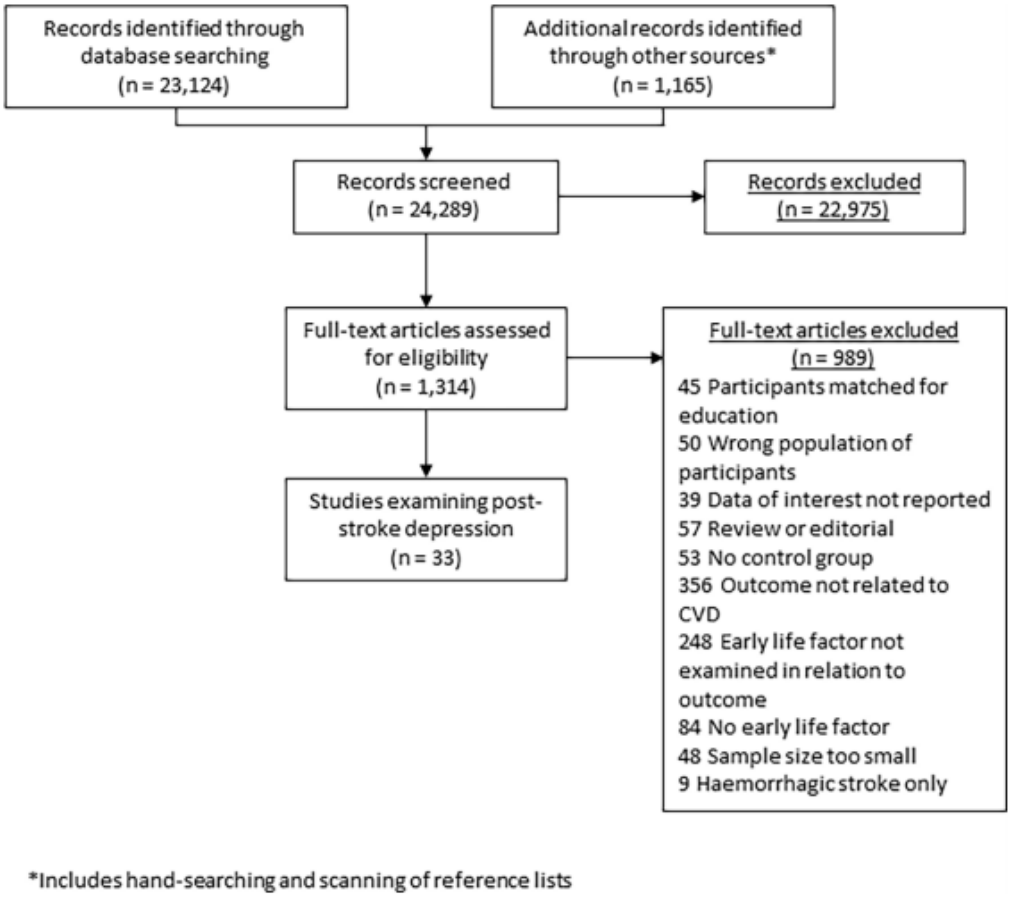

Fig 1. PRISMA flow chart of search process.

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depression. 33 articles, all examining education and post stroke depression met inclusion criteria (see Table 1 for summary of included studies and Table A in S1 File for full details). One of these articles [11] also examined premorbid cognition. There were no studies examining childhood SES and post-stroke depression.

Quality assessment and publication bias

The quality of the included papers was good, with scores from 18-23/24 (median = 20). The main risk of bias was regarding sample representativeness (Figure A in S1 File).

There was no evidence of publication bias among papers examining education level and depression (Figure B in S1 File). Due to the small number of studies, it was not possible to assess publication bias in papers reporting mean years of education or correlation coefficients.

Table 1. Table of studies included in systematic review of early life factors and post-stroke depression.

	Childhood IQ	Education	Childhood SES
Number of papers identified	1	33	0
Number of studies included	1	33	0
Study setting			
Population	0	3	0
Hospital	1	22	0
Community	0	1	0
Outpatient clinic	0	7	0
Total number of participants	205	8,377	0
Total number of depressed patients	37[a]	2,664	0
Total number of non-depressed patients	98[a]	5,460	0
Age range of included studies	72–73	27–85	0
Quality score[b]	20	20 (1.5)	NA
Range	NA	18–23	NA

[a] Data not reported for 2 studies.

[b] Median (interquartile range).

SES: socioeconomic status.

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Premorbid IQ

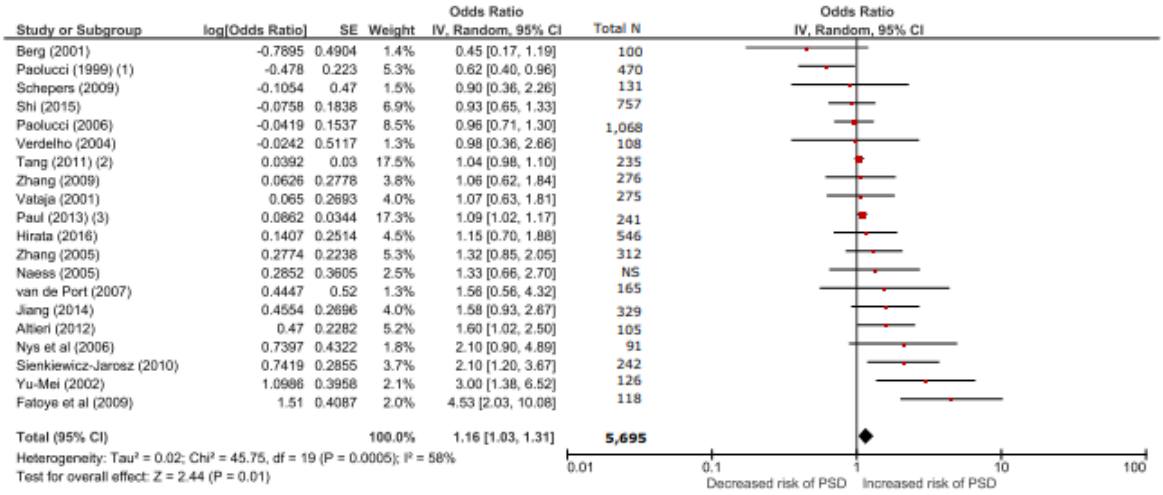
One paper [11] (n = 205) examined premorbid IQ using the National Adult Reading Test Revised (NART-R) and post-stroke depression diagnosed using The Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria (37 post-stroke depression; 98 no depression). NART scores, transformed into an IQ score, were higher (better premorbid IQ) in those without depression (mean: 104.0, SD 10.1) compared to those with post-stroke depression (mean: 101.8, SD 9.8) but this difference was not statistically significant.

Education

Thirty three studies [11–43] (n = 8,377, range: 64–1,068) examined education and post-stroke depression (2,664 post-stroke depression; 5,460 no depression participants, 314 participants not classified) aged 27–85 at follow up. Education level was assessed as duration (i.e. ≤8 years vs >8 years) in 12 studies [12, 17, 19, 21, 24, 27, 30, 32, 33, 33, 34, 36], attainment (i.e. <High School vs ≥High school) in 13 studies [13–16, 18–20, 22, 23, 28, 29, 31, 35, 35] and mean years of education in 8 studies [11, 37–43]. Most studies were conducted in Europe or North America (17 studies) however some were based in the Asia Pacific Region (12 studies), Africa (1 study), the Middle East (2 studies) and South America (1 study). Twenty three studies were based in hospitals, 6 were outpatient studies and 4 were population or community based studies.

Education level and depression. Of the 33 studies 8 papers [24–31] (n = 1785) reported ORs (711 with and 1074 without post-stroke depression) and 12 papers [12–23] (n = 3879) reported frequencies of presence of post-stroke depression by educational attainment or duration (1434 with and 2445 without post-stroke depression) which we used to calculate unadjusted ORs. Three of these studies [26, 27, 30] reported adjusted odds ratios.

Eleven studies [12,13,15,16,20,21–23,25,29,30] (n = 1,937: range = 91–329) defined post-stroke depression according to a cut off score indicating the presence of mild depressive symptoms or above. These were measured on rating scales including the Montgomery Asberg Depression Rating,Scale (MADRAS) (4 studies [15, 16, 20, 25]; score ≥7), the Hamilton



Footnotes
(1) Adjusted for age and sex
(2) Adjusted for sex, lobar CMBs, Lubben Social Network Scale score, Mini Mental State Examn score, diabetes, National Institute of Health Stroke Scale score
(3) Adjusted for age, sex, smoking, income, cognitive dysfunction, activities of daily living

Fig 2. Forest plot comparing low vs high education and risk of depressive symptoms following stroke. OR<1: low education decreases risk post-stroke depression; OR>1 low education increases risk of post-stroke depression. Random effects model.

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Depression Rating Scale (HDRS) (2 studies [21, 23]; score ≥8 mild depressive symptoms), the Becks Depression Inventory (BDI) (2 studies [12, 13]; score ≥10), the Geriatric Depression scale (GDS) (2 studies; Short version [29]: score >5, short version ≥7[30]) and a Chinese self-report depression scale (1 study [22]).

Nine studies [14,17–19,24,26–28,31] (n = 3,754: range = 105–1,068) defined post-stroke depression as a clinical diagnosis of depression or moderate to severe depressive symptoms on a self-report scale. This included four studies [17–19, 24] which classified participants with depression by a diagnosis of major depressive disorder (MDD) according to DSM criteria. Two studies [28, 31] used the Centre for Epidemiologic Studies Depression scale (CES-D) which diagnoses a depressive episode using the DSM criteria. Three studies defined participants with moderate or severe depressive symptoms according to depression rating scales: the Hamilton Depression Rating Scale (HDRS) (score of ≥21, 1 study[27]); the Bengali version of the Geriatric Depression scale (GDS) (score of ≥21, 1 study[26]) and the Patient Health Questionnaire 8 (PHQ-8) (score ≥10, 1 study[14]).

Overall low education (<9 years) was associated with increased risk of post-stroke depression or depressive symptoms (OR 1.16 95% CI 1.03–1.31, p = 0.01, Fig 2). Heterogeneity between studies was moderate (I^2 58%). The 95% prediction interval was 0.98 to 1.52.

Sensitivity analysis

We conducted several post hoc sensitivity analyses examining education level and post-stroke depression (see Figs 3 and 4 and Figures C-J in S1 File.). Definition of post-stroke depression explained some of the between study heterogeneity (χ^2 (1) = 4.47 p = 0.03). Low education was associated with increased risk of post-stroke depression defined as a score of mild and above on a depression rating scale (n = 1,937, OR 1.47 95% CI 1.10–1.97, p<0.01,

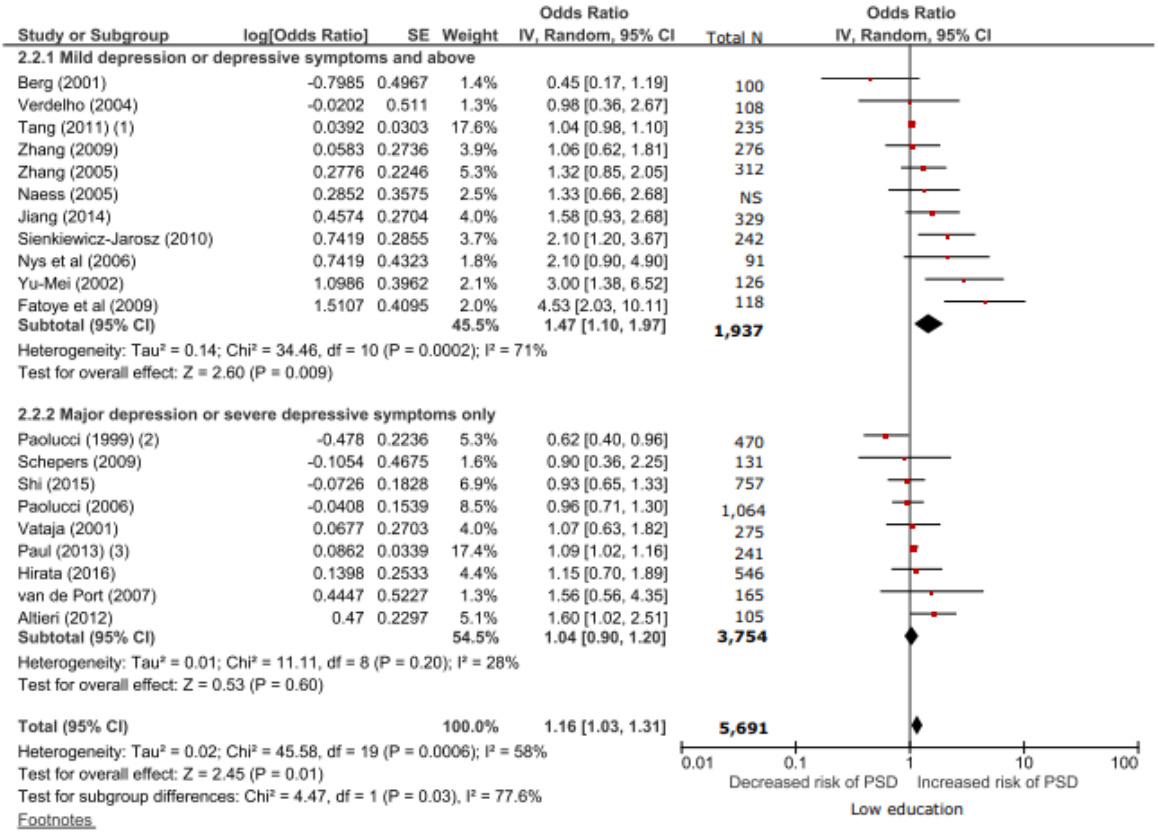

Fig 3. Sensitivity analysis comparing studies with depression defined as mild symptoms and above vs clinical depression or severe depressive symptoms only.

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95% PI 0.47–3.00) but not major depression or severe depressive symptoms (n = 3,754 OR 1.04 95% CI 0.90–1.31, p = 0.60, 95% PI 0.69–1.51) (Fig 3).

Low education was associated with post-stroke depression in studies which did not adjust for age and sex (18 studies, n = 4,984; OR 1.27 95% CI 1.08–1.51, p<0.01, 95% PI 0.95–2.14) but not in studies which did adjust for age and sex (2 studies, n = 711; OR 0.86 95% CI 0.50–1.48 p = 0.58, 95% PI 0.96–1.81) (Fig 4).

The risk of post-stroke depression did not differ according to the depression scale used, participants age (<65 vs ≥65 years), first stroke only vs recurrent or unspecified stroke, past history of depression as an exclusion criteria (yes vs no), time since stroke (≤6 months vs >6 months), study setting (hospital or outpatient clinic vs population-based) and country of origin (Europe or North America vs Asia Pacific region or Africa).

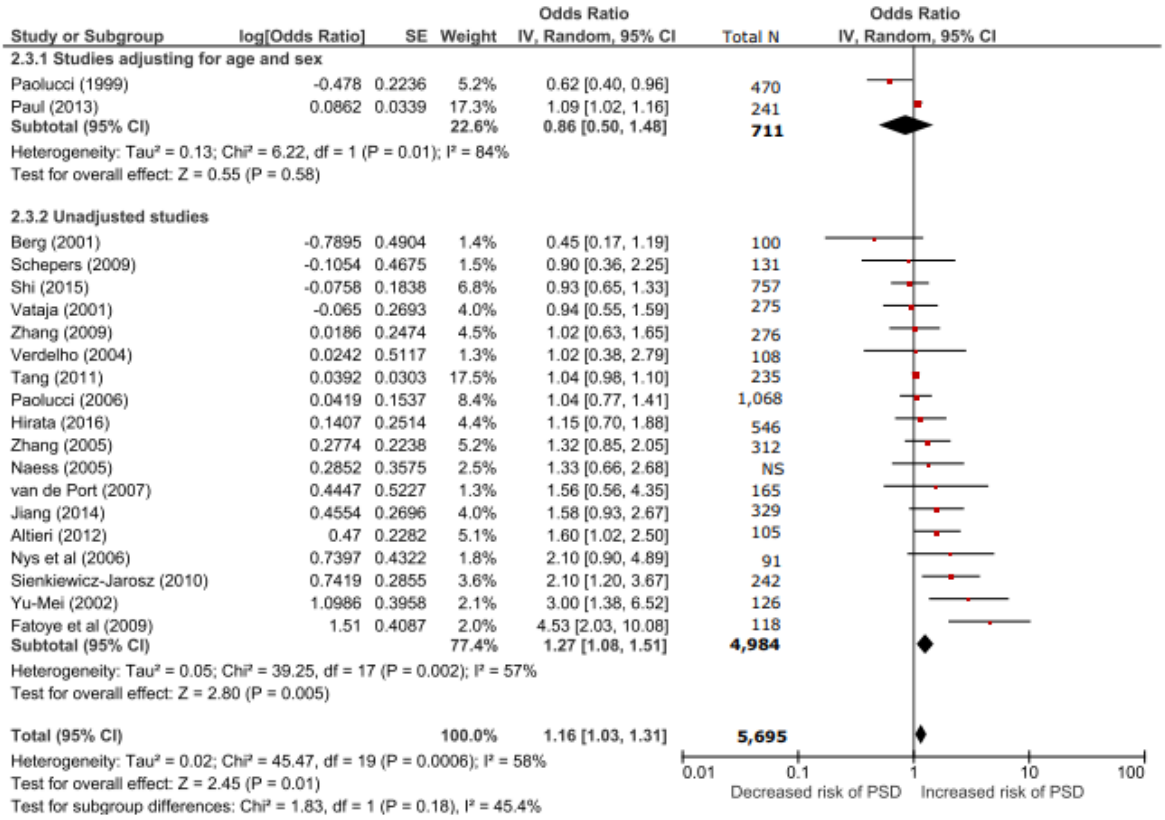

Fig 4. Sensitivity analysis comparing studies adjusted for age and sex vs unadjusted studies.

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Exclusion of the paper [23] with the lowest quality score, or the two studies [20, 25] with unclear definitions of education levels, did not significantly alter the results (OR 1.23 95% CI 1.02–1.49, p = 0.03; OR1.24, 95% CI 1.03–1.50, p = 0.02).

Mean years of education and depression. Of the 33 studies, 7 [11, 37, 38, 40–43] (n = 1943: range = 80–469) reported mean years of education for participants with and without post-stroke depression (273 post-stroke depression and 1251 no post-stroke depression) and one study [39] reported median years of education. Post-stroke depression was diagnosed using the DSM criteria (5 studies[11, 38, 40–42]), and the BDI [37], the GDS [43] and the Hospital Anxiety and Depression Scale (HADS) [39] in one study each. Participants with post-stroke depression had significantly fewer years of education than those without post-stroke depression (MD 0.68 95% CI 0.05–1.31 p = 0.03, Fig 5). None of these papers adjusted for vascular risk factors.

Heterogeneity between studies was moderate (I^2 56%). The 95% prediction interval was 1.14 to 2.50. There were too few studies to conduct any sensitivity analyses.

Correlation between education and depressive symptoms. Of the 33 studies, 5 [32–36] (n = 831: range = 64–300) reported correlation coefficients for education and post-stroke

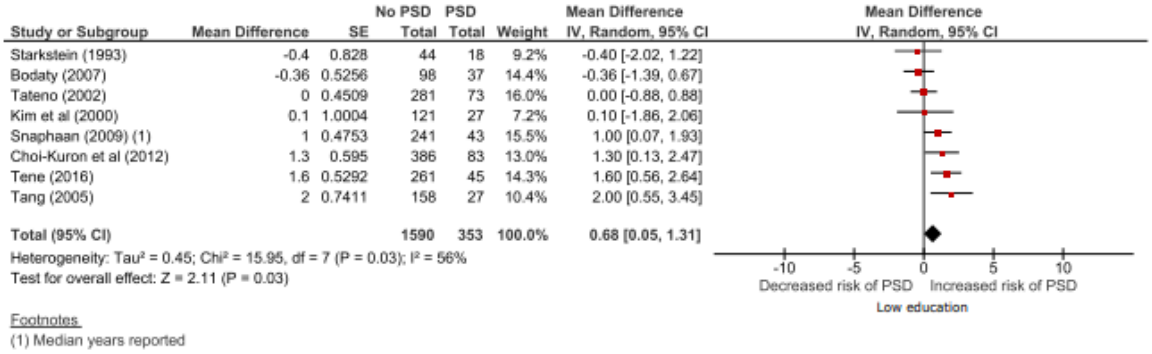

Fig 5. Mean years of education for those with and without post-stroke depression. Random effects model for the mean difference. Negative mean difference = lower education decreases risk of post-stroke depression and positive mean difference = higher education decreases risk of post-stroke depression.

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depressive symptoms at age 56–70. Most studies used years of education while one [35] used educational attainment ranging from 1 (Primary school) to 7 (University degree). One study [35] provided risk factor adjusted results. Depressive symptoms were measured using the HADS in two studies [32, 36], the HDRS [34], the GDS [33]and the CES-D [35] in one study each.

Overall correlation between education and depressive symptoms did not reach statistical significance (r = -0.10 95% CI -0.24–0.04, p = 0.15, Fig 6), although the effect was in the same direction as the effect of the alternative education measures above on post-stroke depression. Heterogeneity was high between studies (I^2 77.3%) but the data were too sparse for sensitivity analyses.

Discussion

Our meta-analysis is the first comprehensive examination of all data on education and risk of post-stroke depression and suggests that longer duration of education is associated with a

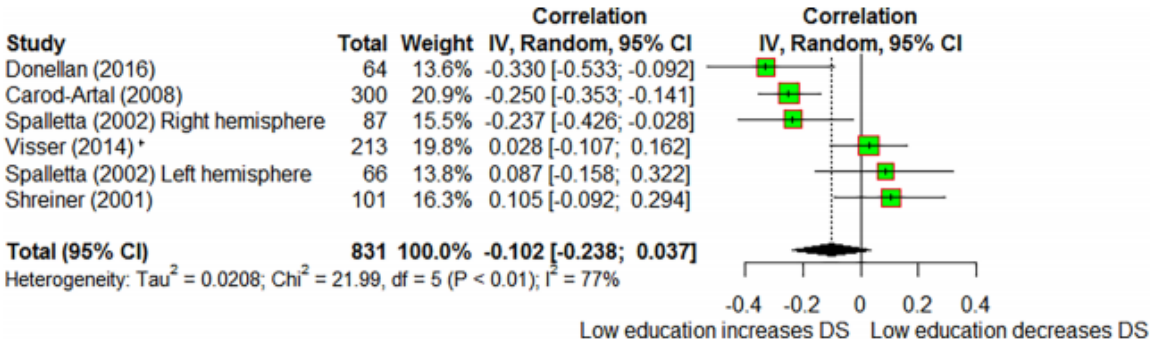

Fig 6. Forest plot showing correlation between education and depressive symptoms in stroke patients. Negative correlation = low education increases depressive symptoms; Positive correlation = low education decreases depressive symptoms. DS = depressive symptoms. * adjusted for sex, income, smoking, age, cognitive dysfunction and activities of daily living. DS = depressive symptoms.

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decreased risk of depression following stroke occurring in later life. Less versus more education was associated with a 16% relative increase in post-stroke depression. This relative risk translates to an absolute increase in post-stroke depression risk of approximately 5.9/1,000 for lower versus higher education but with wide confidence intervals and heterogeneity. Furthermore, participants with post-stroke depression had an average of 0.68 fewer years of education than those without post-stroke depression. These findings suggest important implications for predicting risk of post-depression and of recovery after stroke. A previous review [7] reported significant associations between education and depression in only two of the studies they identified, but only included 10 papers (versus the 33 included here) and excluded studies which did not analyse education directly, which reported mean years or correlation coefficients, and did not include a comprehensive meta-analysis such as performed here.

Our sensitivity analysis showed that low education was associated with increased risk of post-stroke depressive symptoms, defined as mild symptoms and above, but not severe depressive symptoms or a clinical diagnosis of depression. Studies using a cut of score of mild depressive symptoms to define post-stroke depression also included participants with moderate to severe depressive symptoms. Therefore it is unclear whether the association between education and post-stroke depression is stronger for milder depressive symptoms or whether these differences are due to methodological differences between studies. The association between years of education and depression severity was examined in only one study [15], which found no association. However the number of participants with major depression in this study was low (n = 14) and so this should be examined in future studies with larger sample sizes.

The diagnosis of depression in stroke populations is more difficult than in those without stroke and many depression scales were not originally developed for patients with stroke. Stroke patients may suffer from symptoms such as fatigue and lack of appetite after stroke, which may lead to inflated scores on depression scales containing a somatic component (e.g. BDI, HDRS) compared to those that do not include such items (e.g. HADS, MADRAS). No studies adjusted for other common associates of post-stroke depression such as fatigue, although these factors should be considered when conducting research into post-stroke depression. Meta-analysis [44] suggests that the CES-D, HDRS and PHQ-9 are the most promising options to screen for post-stroke depression. However in our review CES-D and the HDRS were only used in three [28, 31, 35], four [21, 23, 27] studies respectively. One study [14] used the PHQ-8 which contains one less question that the PHQ-9.

We found considerable heterogeneity between studies and calculated prediction intervals in addition to confidence intervals. The prediction interval is useful in the presence of heterogeneity as it provides a range of effects that would be expected from a new study with similar characteristics to the current studies [10]. The 95% prediction interval indicates that although low education on average is associated with an increased risk of post-stroke depression, some future studies may not find an association. Specifically in a future study the expected association between education and post-stroke depression would be between 0.98 and 1.52 with 95% confidence.

Confounders were poorly addressed, either because authors reported unadjusted results or because frequency data were used to calculate unadjusted odds ratios. In those papers that did include adjustment for confounders (four studies), there was variation in the number and type used. Of particular importance are sex and age which were adjusted for in four and three studies respectively. Female sex is a risk factor for post-stroke depression [45] and in the cohorts included in this review females may be more likely to have lower levels of education. Similarly older participants may have less education and may be more vulnerable to depression due to more advanced vascular disease. Our sensitivity analysis showed that low education was associated with post-stroke depression in studies which did not adjust for age or sex but there was

no association in studies which did adjust for age and sex, however this included only two studies. Inclusion of the one study [41] that did not adjust for age but did adjust for sex did not alter the results of the sensitivity analysis. Other confounders which were adjusted for include stroke severity (one study) and impairments in activities of daily living (two studies). More studies are needed to examine associations between education and post-stroke depression after adjustment for risk factors for post-stroke depression, particularly age and sex.

No studies adjusted for other early life factors or adult SES. It is likely that education is interrelated with premorbid IQ and that all factors are associated with an increased risk of stroke, but it was not possible to assess the independence of these early life risk factors on post-stroke depression from the current literature as the only paper which examined both premorbid IQ and education reported mean values for each separately. Education is also strongly associated with adult SES which is itself a risk factor for stroke and depression [46]. Previous research has suggested that education and measures of SES such as income may have independent associations with health outcomes [47]. However future studies should examine associations between education and post-stroke depression when controlling for adult SES.

While methodological differences between studies might also contribute to heterogeneity, we were not able to find any evidence that the type of depression scale used, whether set in hospital in-patient, out-patient or population-based, world region, inclusion or exclusion of prior stroke or prior history of depression or patient age accounted for the heterogeneity. Other differences between studies include the interval between stroke and post-stroke assessment which varied from within 48 hours to greater than 18 months. However, prevalence of depression after stroke has been found to be stable across studies conducted at different time points [48, 49] and our sensitivity analysis showed that the effect of education and depression did not differ between before and after 6 months post stroke.

Exclusion criteria varied among studies. Seven studies excluded participants with a pre-stroke history of depression and eight studies excluded participants with a previous history of stroke, both factors which have been identified as risk factors for post-stroke depression[7]. Our sensitivity analyses showed that studies including participants with a history of stroke or depression reported a higher effect of education on post-stroke depression risk than those that excluded such participants, but these differences were not significant. No studies adjusted for history of depression or stroke in their analysis.

The majority of the identified studies were cross sectional. Depressive symptoms may fluctuate over time and a single measurement at a relatively arbitrary point in time may only provide a snapshot of symptoms, particularly mild symptoms. A more comprehensive measure of depressive symptoms at multiple time points may offer a more precise estimate of the association between education and post-stroke depression. Although 11 of the identified studies were longitudinal only 5 reported measures of depression or depressive symptoms at multiple time points in relation to education. In two studies [37,24] low education level was associated with depression measured at baseline, 1 month [24] and 3 months [37]. Another study reported that those whose depressive symptoms worsened between baseline and 6 month follow up were less educated than those whose symptoms stayed the same [43]. However two studies [18,20] found no association between education level and depressive symptoms measured at baseline, 6 months, 12 months [18] and 36 months [20] post-stroke.

The majority of studies were from Europe or North America followed by the Asia Pacific Region. Our sensitivity analysis found no difference between studies conducted in Europe or North America compared to the Asia Pacific Region or Africa. However, we were only able to conduct sensitivity analysis on a subset of papers and social and educational disparities may vary between these world regions.

We excluded studies with less than 50 participants as results from small studies can be less reliable[50]. Therefore, although our funnel plot showed no publication bias, we may have excluded smaller non-significant studies.

Strengths and limitations of the review

Our systematic review had limitations. Resources prevented contacting authors for original data where information on education may have been collected but not reported. The sensitivity analysis was not able to account for all the heterogeneity.

Strengths of the review include a pre-specified published protocol, validated search strategy, double data extraction. We followed published guidelines and used exemplary methods on conduct of systematic reviews and meta-analyses, and established scale for quality assessment which showed an overall high level of study quality. Some sample sizes were small, however there was a reasonable total sample size for many of the analyses producing a comprehensive literature review and meta-analyses amassing data on 8,377 participants. Some analyses lacked power and we may have missed some significant associations through lack of significant data.

Implications and conclusions

The aetiology of post stroke depression is still unclear. Some researchers propose that the primary mechanism linking stroke and depression is biological in which brain damage caused by ischaemic lesions disrupt neural circuits involved in mood regulation. Others propose that depression is caused by dysfunctional psychosocial adjustment following the stroke. It is likely that post-stroke depression is of multifactorial origin and a combination of biological and psychosocial mechanisms.

There are several possible explanations for the observed relationship between education and post-stroke depression. Our previous systematic reviews [5, 6] showed that low education was associated with an increased risk of stroke and subclinical cerebrovascular disease (e.g. white matter hyperintensities). It may be that low education leads to more severe stroke which in turn increases depression. Alternatively, low education may increase imaging markers of vascular disease which increase the risk of depression and stroke since a relationship between WMH and depression is suggested [51].

Our findings show an association between lower educational attainment and increased risk of depression following stroke. However further studies are needed to confirm this and our findings should be interpreted with caution due to the substantial heterogeneity between studies, the relatively large confidence intervals around the effect sizes and the fact that many studies did not adjust for potential confounders. Health disparities have been widely discussed and emphasise the importance of addressing social inequality to improve health outcomes. Post-stroke depression is often considered a treatable complication of stroke, but antidepressants are only partially effective and, despite its high prevalence, it remains poorly recognised and undertreated and trials are ongoing. Identifying additional aspects of the mechanisms of post-stroke depression and modifiable risk factors may lead to more specific therapeutic interventions to target those most at risk and may help design future policy. Future research should examine the combined effect of education and other early life factors on post-stroke depression after adjusting for possible confounders.

Supporting information

S1 Table. PRISMA checklist.
(DOCX)

S1 File. All supporting information.
(DOCX)

S2 File. Data.
(XLSX)

Author Contributions

Data curation: Ellen V. Backhouse, Caroline A. McHutchison, Vera Cvoro, Susan D. Shenkin, Joanna M. Wardlaw.

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Supervision: Joanna M. Wardlaw.

Writing – original draft: Ellen V. Backhouse.

Writing – review & editing: Caroline A. McHutchison, Vera Cvoro, Susan D. Shenkin, Joanna M. Wardlaw.

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